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TITLE:
Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program

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13. SUPPLEMENTARY NOTES

14. ABSTRACT
Background: There is a critical need to increase the number of racially and ethnically diverse prostate cancer researchers. The purpose of this 3-year project is to develop a prostate cancer research training program at the Medical University of South Carolina (MUSC) with 12 students from the following three Historically Black Colleges and Universities (HBCUs) in South Carolina: Claflin University, South Carolina State University (SCSU), and Voorhees College. Students from the three HBCUs (defined as "Student Fellows") will participate in research internships in the laboratories/research units of senior prostate cancer research scientists at MUSC. Specific Aims: Aim 1.) To provide training in the basics of research design and methods to 4 Student Fellows each year through participation in the MUSC Summer Undergraduate Research Program (SURP); Aim 2.) To immerse 4 Student Fellows each year in a prostate cancer research training curriculum. Results: In 2009, four Student Fellows were identified, recruited to participate and admitted to the DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program. The Student Fellows were matched with Research Mentors at MUSC, with whom they conducted research in the summer of 2009. Each Student Fellow prepared a scientific paper and gave a scientific presentation at the end of the Training Program. Each Student Fellow also completed an 8-week Kaplan Graduate Record Examination Test Preparation Course at a local Kaplan Center. A total of 73 students from the three HBCUs attended the Ernest E. Just Symposium at MUSC in February of 2010. Conclusions: In the summer of 2009, we provided state-of-the art comprehensive prostate cancer research education and training opportunities for four Student Fellows from HBCUs in South Carolina. Each Student Fellow prepared a scientific paper and gave a scientific presentation. We are developing a cadre of scientists who are well-prepared to conduct research spanning the continuum from basic science to clinical science to population-based research. The 2010 application process has been completed, and four Student Fellows have been selected to participate in the Training Program during the Summer of 2010.

15. SUBJECT TERMS
Prostate Cancer Research Training Program Summer Undergraduate Research Program (SURP) Student Fellows from Historically Black Colleges and Universities (HBCUs)

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INTRODUCTION

The Scientific Context of the Training Program

The overarching goal of the Training Program is to recruit the next generation of prostate cancer researchers by exposing undergraduate students ("Student Fellows") from Claflin University (CU), South Carolina State University (SCSU), and Voorhees College (VC) to prostate cancer research at the Medical University of South Carolina (MUSC), and training them to meaningfully participate in such research activities. **Basic science and clinical researchers** are needed to aggressively pursue and test better methods to decode the prostate cancer fingerprints, which hold the key to understanding the relationship between gene expression and future prognosis. **Population science researchers** are needed who will identify barriers and facilitators of prostate cancer early detection and treatment, and develop strategies to overcome them. The Training Program will provide a pipeline for future generations of these prostate cancer researchers.

The two Specific Aims are to:
Aim 1: Provide training in the basics of research design and methods to 4 Student Fellows each year through participation in the MUSC Summer Undergraduate Research Program (SURP).

Aim 2: Immerse 4 Student Fellows each year in a prostate cancer research training curriculum.

Program Director and Training Team

Dr. Marvella E. Ford is the Program Director. Drs. Rebecca Bullard- Dillard (CU), Judith Salley (SCSU), and Leroy Davis (VC) are Associate Directors. This four-person leadership team collaborates closely in the management and administration of the award, as well as the continued development and enhancement of the Training Program. The Program Director and Associate Directors share scientific interests in health disparities, serve in other leadership roles within their institutions, and meet frequently, both formally and informally. These individuals form the Executive Committee for the Training Program. Each institution has appointed Faculty Advisors consisting of Dr. Kamal Chowdhury (CU), Dr. James B. Stukes (SCSU), and Ms. Gayle Tyler Stukes (VC).

BODY

Statement of Work

Task 1. Identify and Recruit the Student Fellows

(a) Identify the pool of potential Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)
(b) Interview the potential Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)
(c) Select the top Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)
(d) Match the Student Fellows with Their Research Mentors at MUSC (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)
(e) Hold the Kickoff Intensive and Luncheon (Year 1, months 4-6; Year 2, months 4-6; Year 3, months 4-6)

Task 2. Provide Training in Biomedical and Prostate Cancer Research

(a) Conduct Aim 1: Training in the Basics of Research Design and Methods through participation in the MUSC Summer Undergraduate Research Program (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)
(b) Conduct Aim 2: Prostate Cancer Research Training (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)
(c) Sponsor the Student Fellows' Participation in a Graduate Record Examination (GRE) course (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)

Task 3. Prepare Tangible Scientific Products

(a) Prepare and present scientific abstracts based on the Student Fellows' prostate cancer research (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)
(b) Prepare manuscripts that will be submitted to peer-reviewed journals (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)

Task 4. Evaluate the Training Program

(a) Assess the number of applicants to the Training Program (Year 1, months 1-4, year 2, months 1-4, Year 3, months 1-4)
(b) Assess the number of Student Fellows who apply to graduate school (Year 2, months 1-12, Year 3, months 1-12)
(c) Assess the number of Student Fellows who are admitted to graduate school (Year 2, months 1-12, Year 3, months 1-12)
(d) Assess the number of graduate schools to which Student Fellows are admitted (Year 2, months 1-12, Year 3, months 1-12)
(e) Identify the number of scientific abstracts presented and peer-reviewed publications that result (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)

Task 1. Identify and Recruit the Student Fellows

(a) **Identify the pool of potential Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)**

(b) **Interview the potential Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)**

(c) **Select the top Student Fellows (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)**

To accomplish Tasks 1(a) – 1(c), Dr. Ford, the Program Director worked with Associate Directors Dr. Rebecca Bullard-Dillard (Claflin University), Dr. Judith Salley (SC State University), and Dr. Leroy Davis (Voorhees College) as well as Faculty Advisors Dr. Kamal Chowdhury (Claflin University), Dr. James Stukes (SC State University), and Ms. Gayle Stukes (Voorhees College) to identify potential Student Fellows. The Associate Directors and Faculty Advisors issued a call for applicants to their student bodies and personally approached students whom they felt would be outstanding applicants for the summer research program.

Drs. Ford (Principal Investigator), Bullard Dillard (Associate Director), Salley (Associate Director), and Davis (Associate Director) participated on a conference call in January of 2009. Each Associate Director reported that he/she had successfully identified students to participate in the DOD-funded summer research training program in 2010. Four students (two from Claflin University and two from SC State University) sent drafts of their MUSC Summer Undergraduate Research Program (SURP) applications to Dr. Ford, who edited the applications and returned them to the students and the students' Faculty Advisors. The students then submitted the final applications to the SURP for consideration. All four students were admitted to the SURP and to the DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program.

To broaden the pool of potential applicants, each Associate Director invited faculty and students from his/her institution to participate in the Ernest Just Symposium held on February 26, 2010 at MUSC. A total of 73 students from the three HBCUs attended the symposium (Table 1.). The students who participated in the symposium also received a tour of the MUSC campus and met with MUSC faculty members who could become their future summer research mentors. The DOD grant funds covered travel expenses for two faculty members from Voorhees College who requested travel assistance. All other individuals listed paid for their own travel.

Table 1. 2010 Ernest E. Just Symposium Attendees

Student Names	Institution
Jessica Abercromibe	Claflin University
Brittany Anderson	Claflin University
Meaghen Ashby	Claflin University
LaTisha Clark	Claflin University
Charlyn Daughty	Claflin University
La'Nequa Ferguson	Claflin University
LaQuanna S. Gathers	Claflin University
Emerald Harrison	Claflin University

Table 1. 2010 Ernest E. Just Symposium Attendees	
Student Names	**Institution**
April Haskell	Claflin University
Alquetta Hawkins	Claflin University
Vaughn Heyliger	Claflin University
Neema Hooker	Claflin University
Paul L. Isaac	Claflin University
Daniela Lancaster	Claflin University
Darcel Lancaster	Claflin University
Samona Lawrence	Claflin University
Tamara Planter	Claflin University
Denita Pleasant	Claflin University
Dorea Pleasant	Claflin University
Brittany Orange	Claflin University
Lakya Rice	Claflin University
Bianca Thomas	Claflin University
Ambria Turner	Claflin University
# Students From Claflin University	**23**
Angel Agbatutu	SC State University
Matt Brigmon	SC State University
Gabrielle Dillard	SC State University
Chantal Johnson	SC State University
Shela Mainor	SC State University
Alyssa Murray	SC State University
Anthony Myers	SC State University
Charlencia Owens	SC State University
Janel Randolph	SC State University
Jaquanique Sanders	SC State University
Deanna Seabrooks	SC State University
Cedric Shamley	SC State University
Templeton Tisdale	SC State University
Michael Young	SC State University
# Students From SC State University	**14**
Jasmine Addison	Voorhees College
Michael Akinpelu	Voorhees College
Brittany Allen	Voorhees College
Rashell Blake	Voorhees College

Ceyne Blow	Voorhees College
Kalin Bright	Voorhees College
Blair Britton	Voorhees College
Jennifer Brown	Voorhees College
Nakeya Brown	Voorhees College
Sierra Brooks	Voorhees College
Latoya Brunson	Voorhees College
Jasmine Fields	Voorhees College
Hollie Garnett	Voorhees College
Shantez Givens	Voorhees College
Domonik Hamilton	Voorhees College
Latasha Haynes	Voorhees College
Brittany Horton	Voorhees College
Kemar Hunter	Voorhees College
John Jackson	Voorhees College
Shateria Keel	Voorhees College
David Monely	Voorhees College
Edward McMorris	Voorhees College
Tyquan Parker	Voorhees College
Christopher Reeves	Voorhees College
Celina Ridgeway	Voorhees College
Janay Robinson	Voorhees College
Terea Ross	Voorhees College
Janielle Samuel	Voorhees College
Branton Smith	Voorhees College
Britney Smith	Voorhees College
Phillip Smith	Voorhees College
Romeka Taylor	Voorhees College
Brionca Walker	Voorhees College
Pia West	Voorhees College
Adrian Williams	Voorhees College
Page Williams	Voorhees College
# Students From Voorhees College	**36**
TOTAL # STUDENTS	**73**

(d) Match the Student Fellows with Their Research Mentors at MUSC (Year 1, months 1-3; Year 2, months 1-3; Year 3, months 1-3)

The Student Fellows were matched with their Research Mentors at MUSC based on the expressed interests of the Student Fellows. For example, Ms. Scharan Clarke expressed an interest in clinical research in her application, so she was matched with Dr. Harry Clarke (no relation) a urologist who conducts prostate cancer clinical research at MUSC. Ms. Clarke had an opportunity to shadow Dr. Clarke as he conducted his clinical research. Table 2. shows the names of the students who participated in the 2009 DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program, their Research Mentors at MUSC, and their research topics.

TABLE 2. Summer 2009 DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program Students, Mentors, and Research Topics

Student Name	Academic Institution	MUSC Research Mentor	Research Topic
Ms. Scharan Clarke	Claflin University	Dr. Harry Clarke	Does the Preoperative Evaluation of Men with Bladder Obstruction Affect the Outcomes of Outlet Reduction Procedures?
Ms. Andrea Gibson	Claflin University	Dr. Christina Voelkel-Johnson	Enhancing Gene Delivery tTo Cancer Cells
Ms. Co-Danielle Green	SC State University	Dr. Danyelle Townsend	Role of ABCA2 in Prostate Tumor Progression
Ms. Samantha Jones	SC State University	Drs. Shikhar Mehrotra and Mike Nishimura	Isolation and *Ex Vivo* Expansion of Antigen-Specific CD8+ T cells

(e) Hold the Kickoff Intensive and Luncheon (Year 1, months 4-6; Year 2, months 4-6; Year 3, months 4-6)

The Kickoff Intensive and Luncheon took place during the first meeting of the didactic training program in prostate cancer research, on Thursday, June 4, 2009. The Associate Directors from the partnering institutions gave presentations to the students. Dr. Ford gave an overview of the DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program.

Task 1 Deliverables: Four Student Fellows were identified, recruited to participate in the program, and admitted to the DOD Collaborative Undergraduate HBCU Student Summer Prostate Cancer Training Program. The Student Fellows were matched with Research Mentors at MUSC, with whom they conducted research in the summer of 2009.

Task 2. Provide Training in Biomedical and Prostate Cancer Research

(a) Conduct Aim 1: Training in the Basics of Research Design and Methods through participation in the MUSC Summer Undergraduate Research Program (Year 1, months 6-8; Year 2,months 6-8; Year 3, months 6-8)

The Student Fellows participated in an intensive training program in the Basics of Research Design and Methods through participation in the MUSC Summer Undergraduate Research Program. The 2009 SURP curriculum is included in Appendix A.

(b) Conduct Aim 2: Prostate Cancer Research Training (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)

The Student Fellows participated in an intensive 10-week training program in Prostate Cancer Research. Four lectures focused on population science, one lecture focused on statistical methods in prostate cancer research, four lectures highlighted prostate cancer clinical research, and four lectures emphasized prostate cancer basic science research. Other lectures described funding opportunities available to the students, career development opportunities, qualitative research methods, perspectives of prostate cancer among community members, and tips for preparing graduate school applications. Disparities research was a cross-cutting theme in all of the lectures. Table 3 below illustrates the curriculum. The presentations used by the lecturers are included in Appendix B. Please note that not all lecturers utilized PowerPoint presentations. Some lectures were conducted via roundtable discussion with no slide presentations.

Prostate Cancer Research Training Course			
Week	**Topic**	**Instructor and Organizational Affiliation**	**Location and Time**
Week 1 **Thursday, June 4, 2009**	Introduction to Health Disparities Research	**Rebecca Bullard-Dillard**, **Ph.D.**,CU; **Judith Salley**, **Ph.D.**, SCSU; **Leroy Davis**, **Ph.D.**, VC	HCC Room 121 1:00-2:00pm
Week 2 (Population Science /Epidemiologic Research Lecture) **Tuesday, June 9, 2009**	Vitamin D and Prostate Cancer	**Sebastiano Gattoni-Celli, Ph.D.,** Professor Radiation Oncology	HCC Room 121 1:00-2:00pm
Week 2 (Statistical Methods Lecture) **Thursday, June 11, 2009**	Biostatistical Issues in Prostate Cancer Research	**Elizabeth Garrett-Mayer, Ph.D.,** Director, HCC Statistical Unit, MUSC	HCC Room 121 1:00-2:00pm
Week 3 (Clinical Research Lecture) **Tuesday, June 16, 2009**	Clinical Research Issues in Prostate Cancer: Prostate Cancer Screening Controversies	**Jonathan Picard, PhD**, Assistant Professor, Urology Department, MUSC	HCC Room 121 1:00-2:00pm
Week 3 (Funding Opportunities) **Thursday, June 18, 2009**	Funding Opportunities for Underrepresented Minority Scholars	**Joann F. Sullivan, Ph.D.**, Assistant Dean for Extramural Programs, Director of Grants Development, Professor of Libraries and Information Sciences, MUSC	HCC Room 121 1:00-2:00pm
Week 4 (Basic Science Research Lecture) **Tuesday, June 23, 2009**	Velcade for Injection Therapy for Early Relapsed Prostate Cancer	**Andrew S. Kraft**, **M.D.,** HCC Director, MUSC	HCC Room 121 1:00-2:00pm
Week 5 (Basic Science) **Tuesday, June 30, 2009**	TRAIL Gene Therapy of LNCaP Prostate Cancer Cells	**Christina Voelkel-Johnson, Ph.D.,** Assistant Professor, Microbiology & Immunology MUSC	HCC Room 121 1:00-2:00pm
Week 5 (Population Science Lecture) **Thursday, July 2, 2009**	Employing Qualitative Methods in Research	**Gaynell Magwood, Ph.D.**, Assistant Professor, College of Nursing, MUSC	HCC Room 121 1:00-2:00pm
Week 6 (Clinical Research Lecture) **Monday, July 6, 2009**	Anatomy and the Function of the Prostate	**Harry S. Clarke, M.D.,** Ph.D., Associate Dean for Graduate Medical Education and Professor, Urology Services, MUSC	HCC Room 124 1:00-2:00pm
Week 6 (Clinical Research Lecture) **Tuesday, July 7, 2009**	Pursuing a Graduate Dual Degree Program	**Gabrielle Cannick, DDS, Ph.D**	HCC Room 121 1:00-2:00pm
Week 6 (Basic Science Research Lecture) **Thursday, July 9, 2009**	Prostate Cancer Research: Perspectives of Community Members	**HCC Cancer Disparities Board Members and Jim Etheredge, MPA** Coordinator, HCC Cancer Disparities Program, MUSC	HCC Room 121 1:00-2:00pm
Week 7 (Basic Science Research Lecture) **Tuesday, July 14, 2009**	The present and future for gene and viral therapy of directly accessible prostate and squamous cell cancers of the head and neck	**Jim Norris, Ph.D.,** Chairperson and Professor, Department of Microbiology and Immunology, MUSC	HCC Room 121 1:00-2:00pm
Week 8 (Population Science Lecture) **Monday, July 20, 2009**	Developing Community Coalitions to Combat Health Disparities	**Mr. David Rivers**, Director of Public Information and Community Outreach and Research Associate, MUSC	HCC Room 121 1:00-2:00pm
Week 8 (Population Science/Epidemiologic Research Lecture) **Wednesday, July 22, 2009**	Epidemiologic Issues in Prostate Cancer Research	**Anthony Alberg, Ph.D.,** HCC Associate Director, Prevention and Control Program, Associate Professor, Biostatistics, Bioinformatics, & Epidemiology, MUSC	HCC Room 121 1:00-2:00pm
Week 9 (Tips for Preparing Graduate School Applications) **Tuesday, July 28, 2009**	Improving Graduate School Admission Rates	**Cynthia F. Wright, Ph.D.**, Assistant Dean for Admissions and Associate Professor, College of Graduate Studies, MUSC	HCC Room 121 1:00-2:00pm
Week 9 (Clinical Research Lecture) **Thursday, July 30, 2009**	Clinical Research Issues in Prostate Cancer	**Stephen Savage, M.D.**, Associate Professor, Urology Services, MUSC	HCC Room 121 1:00-2:00pm
Week 10 (Rehearsals) **Tuesday, August 4, 2009**	Research Presentation Rehearsals and Evaluations	**All Research Students** **Dr. Marvella Ford**, HCC **Ms. Melanie Sweat,** Program Coordinator	HCC Room 121 1:00-2:00pm
Week 10 (Socialization) **August 6, 2009**	Culminating Luncheon	**Training Program Student Fellows, Mentors, Lecturers, Staff and Family**	HCC Room 121 1:00-2:00pm

(c) **Sponsor the Student Fellows' Participation in a Graduate Record Examination (GRE) course (Year 1, months 6-8; Year 2, months 6-8; Year 3, months 6-8)**

All four Student Fellows took the 8-week Kaplan GRE Test Preparation Course. The 2009 course schedule description is detailed below in Table 4.

TABLE 4. 2009 KAPLAN GRE TEST PREPARATION COURSE

SESSION	DAY	DATE	TIME
Session 1: Diagnostic Exam & Orientation	Tuesday	June 09, 2009	6:00 PM -8:30 PM
Session 2: Introduction to Math Strategies	Tuesday	June 16, 2009	6:00 PM -8:30 PM
Session 3: Strategic Short Verbal	Tuesday	June 23, 2009	6:00 PM -8:30 PM
Session 4: Arithmetic & Number Properties	Tuesday	June 30, 2009	6:00 PM -8:30 PM
Session 5: Reading I & Issue Essays	Tuesday	July 07, 2009	6:00 PM -8:30 PM
Session 6: Algebra & Data Interpretation	Tuesday	July 14, 2009	6:00 PM -8:30 PM
Session 7: Vocabulary & Short Verbal	Tuesday	July 21, 2009	6:00 PM -8:30 PM
Session 8: Proportions & Geometry	Tuesday	July 28, 2009	6:00 PM -8:30 PM
Session 9: Reading II & Argument Essays	Tuesday	August 04, 2009	6:00 PM -8:30 PM

Task 2 Deliverables: In the summer of 2009, we provided state-of-the art comprehensive prostate cancer research education and training opportunities for **four** students from two of South Carolina's HBCUs. We will develop a cadre of scientists who are well-prepared to play a significant role in discovering and testing new prostate cancer biomarkers. These investigators will conduct research spanning the continuum from basic science to clinical science to population-based research.

Task 3. Prepare Tangible Scientific Products

(a) Prepare and present scientific abstracts based on the Student Fellows' prostate cancer research (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)

(b) Prepare manuscripts that will be submitted to peer-reviewed journals (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)

Each Student Fellow prepared a scientific research paper that will form the basis of a peer-reviewed publication. The papers are included in Appendix C. The Student Fellows are completing manuscripts with their research mentors. Each Student Fellow gave a scientific presentation based on the results of his or her work. Summaries of each Student Fellows' research projects and their PowerPoint presentations are included in Appendix D.

Deliverables: Four scientific papers were prepared by the Student Fellows. Four scientific presentations were given by Student Fellows.

Task 4. Evaluate the Training Program

***(a)* Assess the number of applicants to the Training Program (Year 1, months 1-4, year 2, months 1-4, Year 3, months 1-4)**

As planned, four Student Fellows enrolled in the Training Program in the summer of 2009.

***(b)* Assess the number of Student Fellows who apply to graduate school (Year 2, months 1-12, Year 3, months 1-12)**

All four Student Fellows are currently juniors at their respective institutions, and reported that they have not yet taken the GRE, but plan to take it in their senior year of college.

***(c)* Assess the number of Student Fellows who are admitted to graduate school (Year 2, months 1-12, Year 3, months 1-12) and *(d)* Assess the number of graduate schools to which Student Fellows are admitted (Year 2, months 1-12, Year 3, months 1-12)**

The Student Fellows have not yet applied to graduate schools. They report that they anticipate applying to graduate programs in their senior year of college.

***(e)* Identify the number of scientific abstracts presented and peer-reviewed publications that result (Year 1, months 10-12, Year 2, months 1-12, Year 3, months 1-12)**

Each Student Fellow gave a scientific presentation during the SURP. In addition, the Student Fellows have been invited to submit abstracts to the Innovative Minds in Prostate Cancer Research Today (IMPaCT) conference that will take place in Orlando, FL in March of 2011.

Deliverables: The four Student Fellows who participated in the Training Program in the summer of 2009, all of whom are juniors in college, have stated that they have not applied to or been accepted in a graduate program thus far. All of the Student Fellows reported that they will apply to graduate programs in their senior year of college. Each Student Fellow gave a scientific presentation and submitted a scientific paper as part of the SURP. All of the Student Fellows have been invited to submit scientific abstracts to the upcoming IMPaCT conference in March 2011.

We also asked the Student Fellows to evaluate the Training Program. The results are presented in Table 5. The denominator for the evaluation results is based on data collected from the four DOD-funded Student Fellows as well as two Student Fellows whose funding came from another source. The evaluation forms did not identify which Student Fellows were funded through the DOD, and which were funded through the other source. Therefore, separate analyses could not be conducted for the DOD Student Fellow evaluations. It is important to note that the majority of the Student Fellows rated the program favorably. Only one Student Fellow disagreed that the program helped with learning the fundamentals of prostate cancer research, and would not recommend this program to other students at her college/university. A summary of the analyses is bulleted below.

- 100% (n=6) Agreed/Strongly Agreed that the summer program was a good research experience
- 80% (n=4) Strongly Agreed that the summer program helped them learn the fundamentals of prostate cancer, while 20% (n=1) disagreed
- 100% (n=6) Agreed/Strongly Agreed that the prostate cancer curriculum was interesting and convenient for learning
- 84% (n=5) Agreed/Strongly Agreed that they would recommend this program to other students at their college/university, while 17% (n=1) Disagreed that they would recommend this program to others.

TABLE 5. SUMMARY RESULTS OF STUDENT EVALUATIONS (N=6)					
Survey Item	**Total Strongly Disagree N %**	**Total Disagree N %**	**Total Not Sure N %**	**Total Agree N %**	**Total Strongly Agree N %**
1. Overall, the summer program was a good research experience.	**0 0.00**	**0 0.00**	**0 0.00**	**4 0.67**	**2 0.33**
2. The summer program helped me learn the fundamentals of prostate cancer and research.	**0 0.00**	**1 0.20**	**0 0.00**	**0 0.00**	**4 0.80**
3. The KAPLAN Graduate Record Examination (GRE) Course was effective in helping me to learn GRE test preparation strategies.	**0 0.00**	**0 0.00**	**2 0.33**	**3 0.50**	**1 0.17**
4. The seminar schedule was convenient.	**0 0.00**	**0 0.00**	**0 0.00**	**4 0.67**	**2 0.33**
5. The seminar topics were of interest to me.	**0 0.00**	**0 0.00**	**0 0.00**	**4 0.67**	**2 0.33**
6. Participating in the program helped to strengthen my desire for a career in cancer research.	**0 0.00**	**0 0.00**	**3 0.50**	**3 0.50**	**0 0.00**
7. The Program Director (Dr. Ford) was accessible and assisted me when needed.	**0 0.00**	**0 0.00**	**0 0.00**	**3 0.50**	**3 0.50**
8. The Program Coordinator (Ms. Sweat) was accessible and assisted me when needed.	**0 0.00**	**0 0.00**	**0 0.00**	**1 0.17**	**5 0.83**
9. My research mentor was accessible and assisted me when needed.	**0 0.00**	**0 0.00**	**1 0.17**	**2 0.33**	**3 0.50**
10. I would recommend this program to other students at my college/university.	**0 0.00**	**1 0.17**	**0 0.00**	**4 0.67**	**1 0.17**

KEY RESEARCH ACCOMPLISHMENTS

- Four Student Fellows completed scientific papers describing the results of their summer 2009 research projects.

- Four Student Fellows completed scientific presentations describing the results of their summer 2009 research projects

- Seventy-three students, who are potential Student Fellows from the three HBCUs, participated in the Ernest E. Just Symposium at MUSC on February 26, 2010 and met potential Research Mentors.

- Four Student Fellows completed an 8-week Kaplan Graduate Record Examination Test Preparation Course at a local Kaplan Center.

    - Four Student Fellows have been selected to participate in the Summer 2010 Training Program.

REPORTABLE OUTCOMES

Student Summer Research Summaries

Each Student Fellow prepared a research paper and gave a scientific presentation to their peers, mentors and other faculty on August 6, 2010 at MUSC. Brief summaries of the research projects are described below. The full manuscripts developed by the Student Fellows are included in Appendix C and the scientific presentations are included in Appendix D.

1.) Scharan Clarke, Claflin University

Title: Does the Preoperative Evaluation of Men with Bladder Obstruction Affect the Outcomes of Outlet Reduction Procedures?

Summary: Evaluate whether preoperative workup affects surgical outcomes in patients with symptomatic urinary obstruction. We retrospectively reviewed our series of 119 patients extracted randomly from 2004 to 2009. In our series more invasive preoperative evaluation did not lead to better clinical outcomes.

2.) Andrea Gibson, Claflin University

Title: Enhancing Gene Delivery To Cancer Cells

Summary: Testing HDACi and polymers to see if they will increase infectivity in prostate cancer cells with an adenovirus. The HDACi used are MS275 and depsispeptide and the polymer used is EDGE-3,3'. AdGFP is the adenovirus used in the treatment of cells.

3.) CoDanielle Green, SC State University

Title: Role of ABCA2 in Prostate Tumor Progression

Summary: The objective of my research assignment was to determine if ABCA2 has a role in prostate tumor progression and metastatic phenotype in mouse (TRAMP/ABCA2 knockout) and cell (D6P2T and PC3 knockdown) models. This was achieved by performing specific assays and analyses relating to the ABCA2 knockout models.

4.) Samantha Jones, SC State University

Title: Isolation and *ex vivo* expansion of antigen-specific CD8+ T cells

Summary: T cell immunotherapy is a new approach for using the cells of the immune system to treat prostate cancer. The hypothesis was that CD8+ T cells that are specific for prostate antigens could easily be isolated and expanded from the blood of a female donor. We were successfully able to isolate CD8+ T cells and expand them after making them specific for prostate cancer.

Student Summer Research Manuscript Abstracts

Student Fellows are currently preparing their scientific abstracts for submission to the upcoming IMPaCT conference in March 2011. Each abstract is listed below. Communications between all institutional directors and faculty advisors have taken place to assist the students with their submissions.

Scharan Clarke
Claflin University

ABSTRACT

Does The Preoperative Evaluation Of Men With Bladder Outlet Obstruction Affect The Outcomes Of Outlet Reduction Procedures?

Objective: Evaluate whether preoperative workup affects surgical outcomes in patients with symptomatic urinary obstruction. Noninvasive uroflow and check of post void residual urine has traditionally been adequate assessment for non complicated patients with symptomatic obstruction. We evaluated our series to see if we had clinically significant out come differences. **Methods:** We retrospectively reviewed our series of 119 patients extracted randomly from 2004 to 2009. These patients were selected by procedure code for both electrosurgical resection and photovaporization of the prostate. We found 119 patients who had undergone outlet reducing procedures. **Results:** 68 (57%) underwent electrosurgical resection and 51 (43%) underwent photovaporization of the prostate. The mean preoperative IPSS was 18 with QOL score 3. Thirty two (29%) patients underwent CMG, 35 (32%) underwent noninvasive uroflow, 43(39%) had no preoperative urodynamic testing. The mean PVR was 199mL and 153mL respectively. The mean prostate size was 48cc, 44cc and 52cc respectively. Two patients in each group had incontinence preoperatively 6% for CMG and noninvasive 5% of untested. Retention was present in 9 (28%), 2 (6%), 3 (7%) respectively. Preoperative use of medical therapy was seen in 24(75%), 32(91%), 29(67%) respectively. Operative time was lowest for patients with noninvasive studies with a mean of 55 minutes then CMG at 59 minutes and no studies at 67 minutes. Hospital stay was shortest with noninvasive testing mean of 0.4 days. CMG had a mean of 0.96 days and those with no testing stayed 1.2days. Catheters came out first in those with noninvasive testing mean of 1.2 days, 1.3 with no testing, and 1.9 days with CMG. Two complications were noted in both the noninvasive group and those without testing. Post operatively the mean IPSS was 11.2 in the CMG group, 10 in the noninvasive, and 9.4 in those without studies. This is a change of 9.2, 9.5, 5.6 points respectively. Mean peak flow and PVR were 13ml/sec, and 119cc; 11.7ml/sec, and 118cc; 9ml/sec and 90cc respectively. One patient (2%) had de novo incontinence in the noninvasive group. Five (15%) patients in the CMG group, 4(11%) in the noninvasive, and 1(2%) in the non studied group required recatheterization. Medical therapy was reinstituted in 7 (21%), 4(11%), 1(2%) patients respectively. Mean follow up was 15.7 months in the CMG group, 20 months in noninvasive, and 16 months in those without studies. **Conclusions:** In our series more invasive preoperative evaluation did not lead to better clinical outcomes based on recathterization rates, IPSS, or restarting medical therapy. However, intraoperative complications were more common as was de novo incontinence with less invasive testing.

Andrea Gibson

Claflin University

ABSTRACT

Enhancing Gene Delivery to Cancer Cells

BACKGROUND: Adenoviral delivery to cancerous cells has potential as a new therapy but is also problematic. Many cancer cells lack coxsackie and adenovirus receptor (CAR) which serves as the transduction factor for an adenovirus to enter a cell. HDACi and polymers have been proven to enhance the transduction of an adenovirus. **OBJECTIVE:** This study involves the investigation of a cell line of prostate cancer cells that infects poorly and to test if HDACi or the polymer EGDE-3,3' will increase the infectivity of the cell line. **METHODS:** Infectivity and transgene expression was measured by flow cytometry following exposure to an adenovirus that expresses green fluoresecent proteing. From this, the percentage of cells that were GFP positive were calculated. Also GFP intensity was determined from this as well. **RESULTS:** The results indicate that HDACi increased infectivity in the prostate cancer cells more than 5-fold at MOI's below 10. However EDGE-3, 3' did not increase infectivity. **CONCLUSIONS:** Therefore, EDGE-3, 3' did not work as well as it did in a previous study using bladder cancer cells. HDACi may be more suitable for enhancing adenoviral transgene expression in prostate cancer cells.

CoDanielle Greene
SC State University

ABSTRACT

Role of ABCA2 in Prostate Tumor Progression

Background: Prostate cancer is responsible for an estimated 33% of all newly diagnosed cancers in men. Unfortunately, the tumors caused by the disease do not always respond to the drugs (chemotherapy). Therefore, determining what causes the tumors to become resistant is important to efficiently treat the cancer. **Objective:** This study involves determining the role of ABCA2 expression because it has been associated with resistance to chemotherapy and multi-drugs. The Objectives were to determine if ABCA2 is correlated with tumor progression and to determine whether ABCA2 has an effect on the grade of prostate tumors and instances of metastasis. **Methods:** To examine the objectives, a knock out line was created using the Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) model and compared to wild types by various methods including: Western Blotting Analysis, PCR, MRI imaging, Vimentin and Desmin analyses, Scratch Assays, and Transient Transfections. **Results:** Although prostate tumor progression was similar in both lines, the instances of metastasis were elevated in the knock outs. **Conclusions:** This study increases our understanding of the role of a protein which could indeed be the link to revising treatments so that they will overcome the occurrences of multi-drug resistance and tumor relapse.

Samantha Jones
SC State University

ABSTRACT

Isolation and *ex vivo* expansion of CD8+ T cells

Background: Prostate cancer is one of the leading causes of cancer-related deaths in American men. There are many available therapies for men with localized prostate cancer, which most of the time have serious side effects and negatively affect the patient's quality of life. There are no current treatments for metastatic prostate cancer. There are new ideas for taking an immunologic approach to treating prostate cancer through the use of antigen-specific T cells. The prostate antigen-specific T cells present in the human male body have low affinity and are not adequate enough to create an effective immune response. Because the female human body also contains these prostate-specific T cells, but contains no self antigens because of the absence of a prostate, it was predicted that the affinity of these female donor prostate-specific T cells will be higher than that of the prostate-specific T cells in men. **Hypothesis:** Therefore, our hypothesis is that T cells capable of killing prostate cancer cells are more abundant and have higher affinity in females than males and these T cells can be activated and expanded as a potential therapeutic for prostate cancer patients. **Methods:** To test this hypothesis, we raised and matured DC's from the monocytes of the blood of a female donor. We then pulsed these mature DC's with prostate antigen peptides (PSMA and PSCA) and co-cultured them with purified $CD8^+$ T cells from the same donor. Finally, we analyzed the cultures using flow cytometry for expanded prostate-specific CTLs. **Results:** We were able to raise prostate-specific CTLs using this method and plan to move forward using this method to develop new immune therapies for the treatment of prostate cancer.

CONCLUSIONS

During the first year of the DOD Collaborative Undergraduate HBCU Summer Prostate Cancer Training Program, the tasks outlined in the Statement of Work were met successfully. Two Student Fellows were recruited from Claflin University and two Student Fellows were recruited from SC State University. Each Student Fellow conducted research and prepared a research paper that was presented at the conclusion of the program. It should be noted that the recruitment process for the 2010 Student Fellows is complete, and we have identified four Student Fellows for the Summer 2010 Training Program.

APPENDIX A.

Summer Undergraduate Research Program Lecture Series

Summer 2009

Location: BSB 302, 8:30-9:30 AM

Date	Topic	Lecturer
	Biomedical Ethics – MANDATORY – 9 – 10:50 am	
June 1	Responsible Lab Citizenship **Note time for this day only: 9-9:50 am**	Dr. Ed Krug
June 2	Public Perceptions of Scientific Research – Questionable Research Practices ("And the Band Played On" video and discussion) 9 – 10:15 am	Dr. Ed Krug
	Human Subjects Research (lecture & discussion) 10:20 to 10:50 am	Dr. Susan Sonne
June 3	Moral Reasoning in Ethical Dilemmas (lecture and case study discussion) 9:00 to 9:50 am	Dr. Ed Krug
	Mentoring (lecture and discussion) 10:00 – 10:25 am	Dr. Ed Krug
	Animal Use in Research (lecture & discussion) 10:25 to 10:50 am	Dr. Alison Smith
June 4	Data Management/Data Manipulation (Lecture and case study discussion) 9:00 to 9:50 am	Dr. Ed Krug
	Authorship and Plagiarism (lecture and case study discussion) 10:00 to 10:50 am	Dr. Ed Krug
June 5	Research Misconduct/Whistleblower Protections (lecture and literature discussion) 9:00 to 9:50 am	Dr. Ed Krug
	Closing Comments/Exit Evaluation (10:00 to 10:50 am)	

Outside Assignment: Complete the University of Montana On-Line RCR training (link below) - you must score a minimum of 70% on all quizzes. Submit paper copies of quiz completion to Debbie Shoemaker (BSB102) **no later than 4 PM Friday, June 19**.
(http://ori.dhhs.gov/education/products/montana_round1/research_ethics.html)

June 8	Pub Med	Library Staff
June 9	Developmental Biology	Dr. Kern
June 10	Cell Biology – Tissue Ultrastructure	Dr. Hazen Martin
June 11	Receptors	Dr. Rosenzweig
June 12	Lipidomics	Dr. Del Poeta
June 15	Stem Cells	Dr. LaRue
June 16	C – Cancer Cell Cycle	Dr. Wright
June 17	The Heart	Dr. Halushka

June 18	Confocal Microscopy	Dr. Lemasters
June 19	Microarray Analysis	Dr. Barth
June 22	Proteomics Technology	Dr. Lauren Ball –
June 23		
June 24		
June 25	Recombinant DNA	Dr. Kurtz
June 26	Transcription	Dr. Kubalak
June 29	(H) Arterial Pressure Control & High Blood Pressure	Dr. Halushka
June 30	C – Cytogenetics	Dr. Wolff
July 1	Retinoids & Vision	Dr. Crouch
July 2	G Proteins	Dr. Hildebrandt
July 6	(H) Electrical Properties of the Heart	Dr. Haemmerich
July 7	N - Dementia	Dr. Kindy
July 8	N – ADD/ADHD	Dr. Lavin
July 9	H – Congenital Heart Disease	Dr. McQuinn
July 10	C – Kinds of Cancer	Dr. Gemmill
July 13	H – Imaging the Heart	Dr. Costello
July 14	H – Atherosclerosis	Dr. Hammad
July 15	C – Cancer Chemotherapy	Dr. Kurtz
July 16	N – Addiction & Alcohol	Dr. Corrigan Smothers
July 17	H - Aspirin & NSAIDS	Dr. Halushka
July 20	C – Herbals & Cancer	Dr. Wargovich
July 21	N – Neuroimaging	Dr. George
July 22	C – Epidemiology of Cancer	Dr. Alberg
July 23	C – Pathology Museum	TBA
July 24	N – Neuroimaging lab demonstration	Dr. Mark George
July 27	H – Kidney	Dr. Soltis
July 28	Spinal Cord Injury	Dr. Banik
July 29	Schizophrenia	Dr. Lavin
July 30	N-Addiction & Drugs	Dr. Knackstadt

Note: Lectures in Black are for all students.
Lectures in Blue are for Cardiovascular track students.
Lectures in Red are for Cancer track students.
Lectures in Green are for Neuroscience track students.

APPENDIX B.

Chronological Listing of PowerPoint Presentations By Lecturers

NOTE: Not all lecturers utilized a PowerPoint presentation. Instead, some lectures were conducted through roundtable discussion. Therefore, all lectures may not be presented in this appendix.

"Introduction to Health Disparities Research"

DOD HBCU Collaborative
Summer Undergraduate Research Orientation

Judith Salley, Ph.D. Executive Director
Project EXPORT
South Carolina State University

The MUSC Hollings Cancer Center
Charleston, SC
June 4, 2009

Project EXPORT
South Carolina State University & Medical University of South Carolina

Center of Excellence
on
Metabolic Syndrome and Minority Health

And
The President's Health Initiative at
South Carolina State University

SCSU/ MUSC Project EXPORT Leadership Team

Dr. Judith Salley
Executive Director, SCSU

Dr. Sabra Slaughter
Chief of Staff, PI, MUSC

NCMHD

Mission:

To promote minority health and to lead, coordinate, support, and assess the NIH effort to reduce and ultimately eliminate health disparities.

Health Disparity Defined

Health disparities -
also called health inequalities in some countries, refer to gaps in the quality of health and health care across racial, ethnic, and socioeconomic groups.

Leading Health Disparities

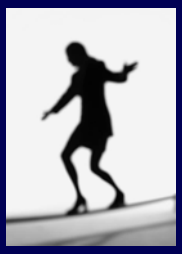
- Access to Health Care
- Mental Health
- Oral Health
- Maternal Morbidity & Mortality
- Infant Mortality & Low Birth Weight
- Immunizations children and adult
- Asthma
- STD's including HIV
- Cancer
- Obesity
- Diabetes
- Cardiovascular Disease

} Metabolic Syndrome

The Metabolic Syndrome: Chronic Disease Crisis

"In every crisis there is a message. Crises are nature's way of forcing change--breaking down old structures, shaking loose negative habits so that something new and better can take their place." -- SUSAN L. TAYLOR

What is the metabolic syndrome?



- A group of risk factors

What are the risk factors?

- High blood pressure
- High blood sugar (diabetes)
  - Many people with diabetes also have metabolic syndrome
- Obesity, especially high waist size
- High triglycerides
- Low HDL cholesterol
  - (HDL is the good type of cholesterol)

Metabolic Syndrome Risk Factors

Obesity
30 lbs. or more overweight

Diabetes
Blood sugar level above 110 mg/dl

Hypertension
Blood pressure above 135/85 mm/hg

Elevated Cholesterol
Above 200 mg/dl

Elevated Triglycerides
Fat in the blood above 200 mg/dl

Waist Circumference
Greater than "40" for men and 35" for women

Why is this important?

- For each risk factor that you have, your risk for heart disease goes up
- If you have all 5 risk factors, you are 6 times more likely to have heart disease

The Metabolic Syndrome and South Carolina State University

- Research Studies
- Educational Training
- Fitness Interventions
- Nutritional Interventions
- Spiritual Interventions
- Infrastructure Changes
- Policy Changes

Clinical Research Unit

In collaboration with MUSC, a fully functioning Clinical Research Unit (CRU) was established at SCSU to engage students and faculty in state of the art clinical investigations in health disparity research.

Four research protocols have been developed and six faculty and staff have served as co-principal investigators.

Metabolic Syndrome and South Carolina State University Freshmen

- 5 Cohorts of SCSU Freshmen completed the Annual Health and Behavior Assessment (over 3,580)
- 25% displayed at least one risk factor for the Metabolic Syndrome
- Obesity was identified as the most prevalent risk factor
- Health Risk Assessments were completed by faculty and staff 2006- 2007

BMI in Freshmen SCSU Students Surveyed

- Average BMI 25.4
- Average BMI for Women 25.0
- Average BMI for Men 26.0

Other Risks Identified in Current SCSU Students

- 2.1% have been diagnosed with high blood pressure
- 1.7 % have been diagnosed with diabetes
- 0.7 % have been diagnosed with high cholesterol

Family History in Current SCSU Students

- Current students reported a history for their mother, father, brothers or sisters:
  - At least 30 % have a family history of high blood pressure
  - At least 4 % have a family history of stroke
  - At least 9 % have a family history of diabetes
  - At least 2 % have a family history of heart disease

President's Health Initiative

The President's Health Initiative (PHI): A novel program launched in 2006 at SCSU that incorporates the health status of undergraduate students, faculty, and staff into initiatives that promote lifestyle changes through education and training to reduce: hypertension, high blood sugar, high cholesterol, and obesity. Outcomes of the various initiatives help transform university policy as it relates to wellness, research, and community outreach.

PHI Health Interventions IMPACT

- Walk for Your Health Club
  (**395** faculty, staff campus participants with pedometers)

Campus Wide Health Screenings (**532**)

Fitness Boot Camps
14 camps totaling **4344** visits since April 2007)
(1478 visits by faculty, staff, students • Feb-May 2009)

- Walk to Work Week April 2007, (over **5,000** faculty staff, students)
- Project HELP- DASH Diet Research Study
  (**60** faculty, staff, students (Summer 2007, Spring 2008)

President's Health Initiative

6 AM Student Boot Camp

President's Health Initiative

6 AM Faculty, Staff, Students Boot Camp "Fit For A King"

The President's Health Initiative IMPACT

Health Status

Project Title	# Participants	Weight Loss	BMI	Blood Pressure	Cholesterol Level
Project HELP	28	>500lbs	Decrease	Decrease	Decrease
Walk for Your Health	15* 3 times/wk	Decrease	Decrease	Decrease	Decrease
Project HELP for Students	30	>130lbs	Decrease	Decrease	Decrease

The President's Health Initiative

Outreach Component

Goal: To raise awareness about Health Disparities (Metabolic Syndrome)

To empower African Americans to take charge of their health

"Know Your Numbers Campaign"

The President's Health Initiative (PHI) "On The Road" Team

Dr. Judith Salley
Executive Director

Joseph McLeod
Program Manager

Dr. James Stukes
Education Core Director

Jeannette Jordan, RD, CDE
Nutrition and Health Educator Consultant

Major Thomas Hundley
Fitness Trainer Consultant

President's Health Initiative

OUTREACH

- Community Outreach Presentations and Screenings
- Local, State, and National Conferences

The First National Conference on Health Disparities was held - July 19-21, 2007- Charleston, South Carolina

Title I Chapter I Parent Advisory Council – 4 conferences
National Sponsored Program Administrators – 2 conferences
SCSU National Alumni Association -1conference

What you can do to decrease your risk

- Develop Healthy Eating Habits
- Keep your weight down or lose weight if you are overweight
- Consistent Exercise Regimen

CONCLUSION

Challenges

USC study: Cancer deaths for state's blacks top national average

- *Blacks are more likely to die of cancer than whites in the Palmetto State and at rates well above the national average, University of South Carolina officials said Tuesday, announcing new findings that mirror other studies on racial disparities in cancer cases*

CONCLUSION

Opportunities

- *"The first step is identifying the fact that the disparities exist and trying to determine if we can look at any particular parameters that show us where they exist more than others," said Diane Gluck, board president of the South Carolina Cancer Alliance. "I think we have a pretty good picture now of what's going on. What we don't have is a good picture of why."*
- *"We need to do more research to deepen our understanding about what's happening and make it possible for public health officials and clinicians to start targeting their activities at the places where it's going to make the most difference," Herbert said*
- *The largest racial disparities were among deaths from prostate, oral and female breast cancers — three categories where blacks in South Carolina die at rates at least 10 percent higher than the national average, the data shows.*

CONCLUSION

Opportunities

Your research experiences this summer is PRICELESS

Developing an Educational Intervention for Rural African-American Female Diabetics – An Overview

by Leroy Davis, Ph. D.

DOD HBCU Collaborative
Undergraduate Research Lecture
June 4, 2009
Medical University of South Carolina

Project Staff

- Center of Excellence in Rural and Minority Health (Voorhees College)
  - Leroy Davis, Ph. D.
  - Gayle Tyler-Stukes, MPH
  - Mary Cave, B.S.
- Family Health Centers, Inc.
  - Gayle Washington, M. D.
- Funding
  - Centers for Disease Control and Prevention (CDC)

Purpose

- To assess quality of life and mental distress issues in a small population of rural African-American female Type 2 diabetic patients
- To develop an intervention tool to help ameliorate the identified issues and improve patients' overall quality of life

The Need

- Diabetes and its treatment, complications, and health conditions can decrease patients' health related quality of life.
- Adopting healthful habits, eating a balanced diet and managing drug therapy can create emotional distress for diabetic patients.
- Understanding how African- American women in rural areas cope with Type 2 diabetes is especially important since this population, most often, must also cope with other psychosocial, economic, and cultural stressors.

The Need (continued)

- Depressive symptoms are common among patients with diabetes (18-35%).
- Compared with patients with diabetes alone, patients with diabetes and comorbid depression display higher functional impairment, work loss and poor self-management behavior.

Methodology

A. Assessing Quality of Life
   - DQoL (short form) scale (15 vs 60)
   - QoL Questionnaire (QoL and depression)

B. Assessing Depression
   - Center for Epidemiologic Studies Scale (CES-D)

C. Focus Groups

D. Developing an Intervention Tool

Preliminary Findings

- Patients screened: 18 (Goal 15-25 sample)
- Age range = 23-73
- Residents of Bamberg, Barnwell and Allendale counties

Preliminary Findings (continued)

- Quality of Life
  - >75% of patients indicated that if they did not have diabetes, the following would be "a great deal better":
    - Employment/career opportunities
    - Social life
    - Family relationships
    - Motivation to achieve things
    - Sex life
    - Enjoyment of food

Preliminary Findings (continued)

- Depression Scale
  - > 60% of patients felt the following most or all of the time (previous week):
    - Fearful
    - Felt I was just as good as other people
    - Felt hopeful about the future
    - Enjoyed life

Ongoing and Future Efforts

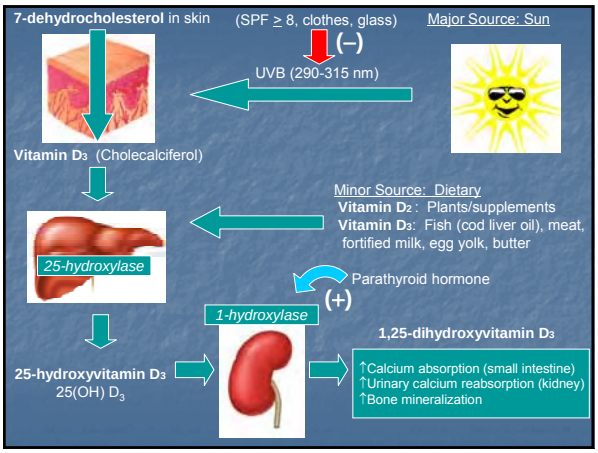
- Patient screenings – through June 2009
- Focus groups (2) – July 2009
- Intervention Development – August through October 2009

QUESTIONS?

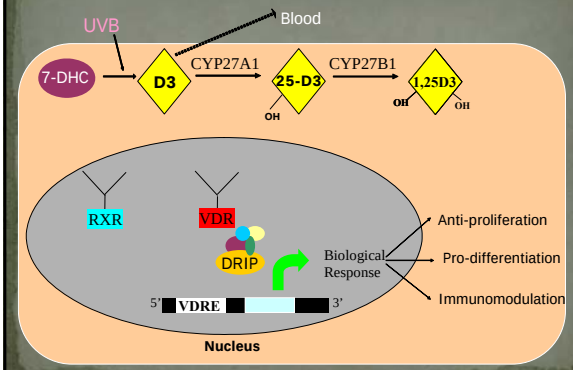
- For further information, I can be contacted at ldavis@voorhees.edu

Vitamin D and Prostate Cancer

Sebastiano Gattoni-Celli, M.D.
David T. Marshall, M.D.
Department of Radiation Oncology - MUSC



Vitamin D3 pathway in SKIN



Vitamin D and Prostate Cells

- Human prostate cells express the vitamin D receptor
- Normal prostate cells also synthesize 1,25(OH)2 D_3 (calcitriol)
- Prostate-derived calcitriol seems to remain sequestered in the gland
- 1,25(OH)2 D_3 can inhibit the proliferation of prostate cancer cells both *in vitro* and *in vivo*

Mechanisms of Action of Vitamin D

- Vitamin D activates protein phosphatase 2A (PP2A)
- Vitamin D induces the expression of insulin growth factor binding protein-3 (IGFBP-3), which increases the levels of the cell-cycle inhibitor p21
- Vitamin D represses the expression of COX-2, the key enzyme for the synthesis of prostaglandins, mediators of inflammation and thought to be important for cancer progression

Mechanisms of Action of Vitamin D (continued)

- Vitamin D decreases matrix metalloproteinases and cathepsin activities, while increasing the activities of their counterparts, tissue inhibitors of metalloproteinase-1 and cathepsin inhibitors
- Vitamin D inhibits the stress-activated protein kinase p38, an activator of the pro-inflammatory cytokine interleukin 6, implicated in the initiation and progression of prostate cancer
- The vitamin D receptor may recognize cognate vitamin D response elements present within the regulatory sequences of hundreds of human genes

Adequate Intake of Vitamin D

- The current recommended daily intake (RDI) is 400IU
- Vitamin D RDI is way too little for good health
- Melanin protects African-Americans from skin cancer
- Melanin prevents vitamin D production in the skin
- This can be remedied by supplementation
- **The desirable level of vitamin D in blood is at least 40ng/mL**
- This can be easily achieved by taking 4000IU/day

Subj#	Age	vit D	PTH	total spine T	total hip T	hip neck T	comments
A001	54	14.5	60.4	-2	-1.7	-1.6	S-osteopenia
A002	53	21	84.8	0	-0.2	-0.9	
A003	54	20.5	42.1	-0.7	-0.7	-1.3	
A004	56	19.2	39.3	-0.2	-1.1	-2.1	H-osteopenia
A005	51	19.1	40.8	-1.8	-0.6	-1.7	S-osteopenia
A006	56	11.9	53.1	-1.6	-0.4	-0.8	S-osteopenia
A007	60	18.9	39.7				no dexa - pt.exceeded w eight limit
A008	50	10.6	53	-3.3	-1.3	-2	S-osteoporosis; H-osteopenia
A009	58	16.9	50.9	-1	-0.4	-1.3	
A010	57	12.1	63.3	1.4	-0.4	-0.6	
A011	62	24.6	63.5	-1.6	-0.8	-1.2	S-osteopenia
A012	51	31.4	40.4	0	0.1	-1.2	
A013	53	34	55.9	-1.3	-0.1	-1	S-osteopenia
A014	54	14.3	71.5	0.2	0.7	0.1	
A101	63	14.7	67.1	-2.1	-0.3	-1.3	S-osteopenia
A102	55	14.5	36.1	-0.9	0.2	-0.5	
A103	53	15.9	34.2	-1.9	0	-0.7	S-osteopenia
A104	56	11	105	-0.1	0	-0.7	
A105	56	6.9	110	-2.6	-1.3	-1.9	S-osteoporosis; H-osteopenia
A106	52	24.5	56.1	-1.5	0.1	-0.4	S-osteopenia
A107	60	9.1	42.3	0.8	0.2	-0.4	

Design of Prospective Study

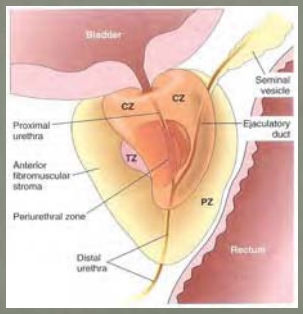
- Enroll 80 male subjects diagnosed with early-stage, low-risk PCa, a serum PSA value of ≤10.0 ng/ml, and a Gleason score of 6 or less (FDA IND 77,839)
- All subjects will have decided to be monitored through active surveillance for at least one year, before deciding whether or not to undergo definitive treatment (surgery and/or radiation therapy)
- Primary Objective: To test the hypothesis that a daily dose of vitamin D3 (4,000 IU) taken for 12 months will result in a decrease serum PSA levels in a significant number of enrolled subjects
- Secondary Objective: To compare prostate biopsy specimens (% positive cores) pre- and post-treatment

Visit	1 Screening	2 Enrollment	3	4	5	6	7	8 Termination
Week	**0**	**0**	**+8**	**+16**	**+24**	**+32**	**+40**	**+48**
[Window]		+1-7 days	±7days	±7days	±7days	±7days	±7days	±7days
ICD	X							
Brief PE	X							X
BP/HR	X		X	X	X	X	X	X
Past Medical History	X							
Inclusion/Exclusion Criteria	X	X						
Labwork:								
*BMP, *serum phosphorus	X		X	X	X	X	X	X
CBC /diff w	X		X	X	X	X	X	X
PSA	X		X	X	X	X	X	X
PTH	X		X	X	X	X	X	X
25(OH)D	X		X	X	X	X	X	X
*Urine Ca/Creat ratio	X		X	X	X	X	X	X
Food Frequency (FFQ)		X						
Adverse event		X	X	X	X	X	X	X
Concomitant meds/ supplements	X	X	X	X	X	X	X	X
Dispense study drug		X	X	X	X	X	X	
Med compliance			X	X	X	X	X	X
****Prostate Biopsy**								

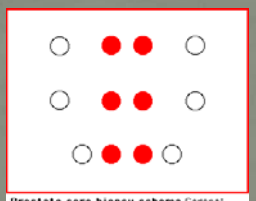
Current Status

- Thirty five subjects have been enrolled thus far
- One subject was terminated because he was diagnosed with colorectal cancer shortly after enrollment; a second subject was taken off study because his PSA rose to >10ng/mL serum; and a third subject was not compliant
- No toxicity was observed or recorded with any of the subjects

Anatomy



Diagnostic Work-Up



Prostate core biopsy schema Coronal prostate plane depicts a 12 core biopsy scheme. Filled circles represent standard sextant sites, while open circles represent additional lateral sites within the gland for extended biopsies.

	Pre-Study Results			Post-Study Results		
Subject # (age)	25(OH)D	PSA	Bx: + cores (Total 12 cores)	25(OH)D	PSA	Bx: + cores (Total 12 cores)
2 (57)	57.69	3.46	**1** (+2 PIN)	67.5	3.64	**0**
4 (69)	12.6	3.98	**4** (+1 PIN)	51.1	4.55	**0** (1 PIN)
6 (67)	32.3	3.33	**6**	63.3	3.76	**5**
8 (68)	17.1	5.65	**2** (+1 PIN)	84.8	4.94	**5**
11 (57)	24.3	3.57	**1**	50.6	4.53	**0**
12 (65)	17.3	6.28	**2**	65.9	7.11	**3**
14 (69)	30.4	1.5	**1**	50.7	0.98	**0**
15 (69)	35.5	0.75	**1**	69.3	0.67	**2**
17 (62)	35.4	4.13	**2**		4.83	**4**

Bx: Biopsy
PIN: Prostatic Intraepithelial Neoplasia

Preliminary Conclusions

These preliminary observations support the use of high-dose vitamin D_3 supplement as a chemo-preventive agent, especially in men with early-stage, low-risk prostate cancer

Acknowledgments

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- Supported by the Gateway for Cancer Research

Biostatistics in Prostate Cancer Research

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June 11, 2009

Statistics

- Statistics is the art/science of **summarizing data** and **quantifying evidence**
- Better yet…summarizing data so that non-statisticians can understand it
- Scientific investigations usually involve collecting a lot of data.
- But, at the end of your study, what you really want is a "punch-line:"
  - Did the new treatment work?
  - Are the two groups being compared the same or different?
  - Is the new method more precise than the old method?
- Statistical inference is the answer!

How do statisticians help research?

- Statistics should be a part of the study from the very beginning
- Statistical issues arise in:
  - Study Design
  - Analysis
  - Interpretation of results
  - Conclusions

What we do

- We plan
- We estimate
- We test

What we do

- We plan
  - we help to plan clinical trials and other kinds of studies
  - we help figure out how many people to study
- We estimate
  - we determine what the "response rate" was
  - we estimate how much better treatment A is than treatment B
- We test
  - we determine which treatment is better
  - we quantify how much better using a test.

Clinical Research in Prostate Cancer

- Research requires a plan
- A DETAILED plan called a "clinical trial protocol"
  - could also be an intervention
  - could also be an observational study
  - but, for simplicity, we focus on a "treatment trial"
  - Example: Velcade for treatment of men with relapsed prostate cancer

Clinical Trial Protocol

- Variety of templates
- Some key elements
  - Specific Aims: you must state what your goals are in terms of measurable objectives
  - Background/Rationale: explanation of why this study is important, what preliminary data exists and justification of the dose.
  - Experimental Design: Describes how the study will proceed. no detail can be spared. someone else should be able to implement the study with no questions.
  - Analysis Plan: how will the data will handled and objectives answered.

Clinical Drug Trial Checklist.

1 *Study Title*
2 *Study personnel*
3 *Rationale*
4 *Objectives*
5 *Study Plan & Schedule of Assessments*
  5.1 *Methods of collecting data*
  5.2 *Study Plan*
  5.3 *Schedule of Assessments*
6 *Inclusion CriteriaA*
7 *Exclusion Criteria*
8 *Prohibited Drugs and Interventions.*
9 *Study design and analysis*
  9.1 *Randomisation*
  9.2 *Power calculations*
  9.3 *Data to be analysed*
  9.4 *Analysis populations*
  9.5 *Withdrawals (protocol violations, broken blinding, withdrawal)*
  9.6 *Statistical Analysis*
  9.7 *Interim analyses*
10 *Safety: Reporting of Adverse Events*
  10.1 Definition of adverse events provided
  10.2 Investigator's responsibility to report adverse events
  10.3 Definition of serious adverse events in accordance with standard criteria
  10.4 Investigator's responsibility to follow-up and characterise adverse events
  10.5 Procedures for informing CDTC/RIEC of adverse events reports
11 *Pharmacy issues: drug storage, dispensing and labelling*
12 *Administrative issues*
13 *Compliance With Good Clinical Practice, Ethical Considerations & Informed Consent*

Endpoint selection

- What measures should we take to determine if our treatment (e.g. Velcade) has worked?
- Example: for each patient, determine if his disease has
  - regressed?
  - stayed the same? ('stable disease')
  - progressed?
- Common endpoints in prostate cancer clinical trials
  - PSA (prostate specific antigen), a biomarker
  - tumor size/volume
  - pain
  - quality of life
- It is important to use endpoints that everyone else uses.

Statistical Design Issues

- Choose most efficient design
- Consider all aims of the study
- Particular designs that might be useful
  - Cross-over
  - Pre-post
  - Factorial
- Sample size considerations
- Interim monitoring plan

Example: prostate cancer clinical trial

- TAX327: Aventis study
- Patient Population: *hormone refractory metastatic prostate cancer*
- Large randomized clinical trial
  - docetaxel, schedule 1
  - docetaxel, schedule 2
  - mitoxantrone
- Primary endpoint: overall survival
- Additioanl Aim: how is PSA related to overall survival?
  - prostate specific antigen
  - well-known 'surrogate' for prostate cancer presence
  - well-known 'test' for prostate cancer progression
- Additional Aim: compare quality of life in the three treatment arms

Study design

- Patients are randomized to one of three arms
- Equal chance of assignment to each arm
- Overall survival:
  - Time from randomization until death
  - Patients are followed until death
  - For patients who do not die by study end, we say that their outcomes are 'censored' at the last known time they were still alive (more on that later)
- Statistician worked with the clinicians to determine how many patients were needed
  - depends on how certain we want to be about our conclusion
  - the expected survival in each group
  - how long patients are followed
  - how long it takes to enroll patients

Analysis Plan: Part of the Design!

- Statistical method for **EACH** aim
- Account for type I and type II errors
  - these quantify how certain we want to be about making mistakes
  - type I: the probability of concluding that there is a difference in treatments when there truly is no difference
  - type II: the probability of concluding that there is no difference when there truly is a difference
- Stratifications or adjustments are included if necessary
- Simpler is often better
- Loss to follow-up: plan for missing data

Estimation

- At the end of the study, you need to be able to "measure" how things went
- Some examples:
  - what proportion of patients responded to the treatment?
  - how many patients are still alive at 5 years?
  - what is the difference in the response rate between the two treatment groups?
  - how much improvement was seen in quality of life from the beginning of the study to the end?
- Estimation depends on the endpoint selection

Estimation in TAX 327

- Outcome of interest is overall survival
- We can estimate
  - median survival: the time at which 50% of patients are still alive
  - 5 year survival: the proportion of patients that are still alive at 5 years
- These are called "point estimates"
- Other aims?
  - the mean change in quality of life from baseline to follow-up
  - the proportion of men with increased PSA at end of treatment

Median survival

- Docetaxel every 3 wks: Median survival = 19.4 months
- Docetaxel weekly: Median survival = 18.7 months
- Mitoxantrone: Median survival = 16.6 months
- Which looks to be the best?

Another key part of estimation

- Precision: how certain are we of our point estimates?
- Variance or standard errors are important!
- We often use 'Confidence intervals" to describe our certainty in our estimates
- A 95% confidence interval: provides an interval that we are 95% certain contains the true parameter estimate
- 95% is most common, but we also see 90% and 99%.

Confidence intervals for Median survival in TAX327

	n	median	0.95LCL	0.95UCL
Doce Q3	241	19.4	17.6	21.6
Doce wk	217	18.7	16.3	21.2
Mitox	228	16.6	14.3	18.6

How to interpret these?

Testing

- Critical for these types of comparative studies!
- The drug company (and everyone else) wants to know if its drug is better than the old drug
- We test hypotheses:
  - hypothesis 0: survival is the same in the three groups
  - hypothesis 1: survival is different in the three groups.
- Depending on the type of outcome, we use different tests
- hypothesis 0 is called the "null"
- hypothesis 1 is called the "alternative"

Outcome of test: p-value

- The most common measure of whether or not the treatments are different is the 'p-value'
- The p-value is the probability of observing the difference we did (or larger) *if the null hypothesis is true.*
- If the p-value is small, it means that the observed data is unlikely if there is really no difference
- If the p-value is large, it means that the observed difference is too small to provide evidence of a "real" difference
- Standard threshold for "significant" p-value?

TAX327

- The 'logrank test' is a type of test we use for testing overall survival
- The p-value for testing that all groups are the same is 0.007
- The p-value testing that survival in the Doce Q3 arm is the same as the Doce every week arm is 0.37
- The p-value testing that survival in the Doce Q3 arm is the same as the Mitox arm is 0.009
- The p-value testing that survival in the Doce every week arm is the same as the Mitox arm is 0.10

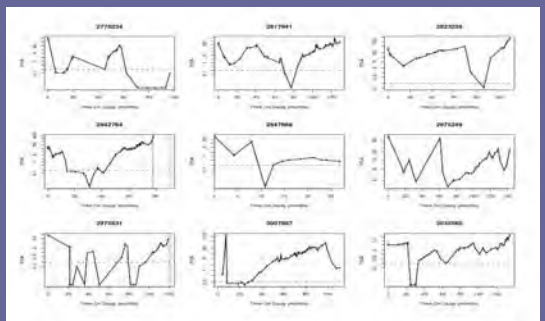
Additional biostatist issues in prostate cancer research

- Measure of 'response'
- Measuring time to progression or time to death

Prostate Specific Antigen

- **Prostate specific antigen** (**PSA**) is a protein produced by the cells of the prostate gland.
- PSA is present in small quantities in the serum of normal men, and is often elevated in the presence of prostate cancer and in other prostate disorders.
- A blood test to measure PSA is considered the most effective test currently available for the early detection of prostate cancer, but this effectiveness has also been questioned.
- Rising levels of PSA over time are associated with both localized and metastatic prostate cancer.

Prostate Specific Antigen (PSA)



Tricky issues with PSA

- Change in PSA from baseline to post-treatment
- Potential problems
  - There is variability due to things other than cancer
    - day to day fluctuations
    - assay sensitivity
    - other prostate disorders
  - When you sample may give you different answers
  - Some question whether or not PSA is a good "surrogate measure"

Surrogate measure

- What is the gold-standard measure in cancer treatment?
- Multiple choice:

A. time from treatment until disease goes into remission
B. time from diagnosis until disease progresses
C. time from treatment until death
D. time from diagnosis until death
E. time from treatment until disease progresses
F. time from diagnosis until disease goes into remission

Surrogate measures in cancer research

- We generally assume the following:
  - if we can shrink the tumor, we can extend life
  - if we can delay tumor progression, we can extend life
- Are these valid assumptions?
  - sometimes yes, sometimes no
- Tumor shrinkage ("clinical response")
  - tumor response is often considered a poor surrogate
- Time to progression
  - tumor progression is often valid surrogate
  - however, it is hard to measure

RECIST criteria

- RECIST criteria offer a simplified, conservative, extraction of imaging data for wide application in clinical trials. They presume that linear measures are an adequate substitute for 2-D methods and registers four response categories:
  - CR (complete response) = disappearance of all target lesions
  - PR (partial response) = 30% decrease in the sum of the longest diameter of target lesions
  - PD (progressive disease) = 20% increase in the sum of the longest diameter of target lesions
  - SD (stable disease) = small changes that do not meet above criteria

http://imaging.cancer.gov/clinicaltrials/imaging/

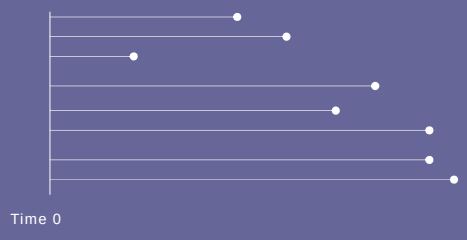
Potential Problems with RECIST

- Stable disease includes both improvements and worsening
- Tumors are 3-D. RECIST only allows for 1-D. Measures are hence fraught with measurement error.
- Tumors with minor differences (e.g., 32% decrease and 28% decrease) are categorized differently.

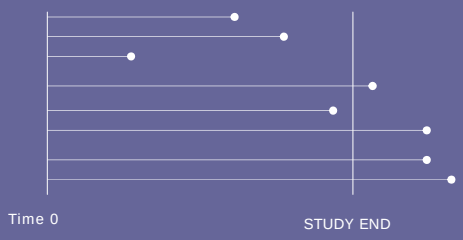
Time to event outcomes

- In cancer research, we are usually interested in measuring time until an event occurs
- the event is usually bad so we are trying to prevent the event from occuring
- inevitably, at the end of the study, many patients will not have had the outcome.
- This is called 'censored'
- More specifically, "right censored"

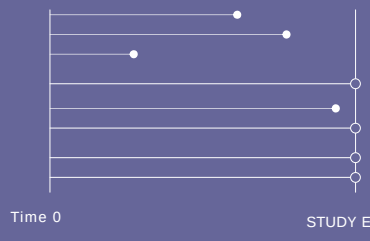
Simple example:



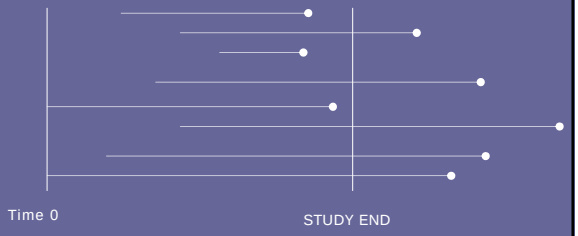
Introduce “administrative” censoring



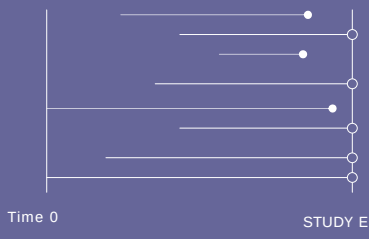
Introduce “administrative” censoring



More realistic: clinical trial



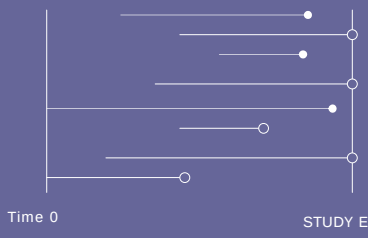
More realistic: clinical trial



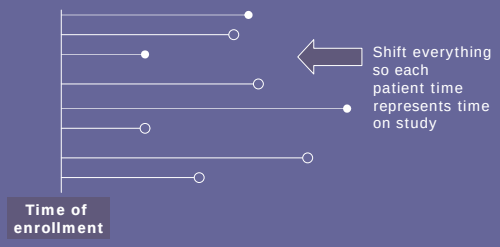
Additional issues

- Patient drop-out
- Loss to follow-up

Drop-out or LTFU



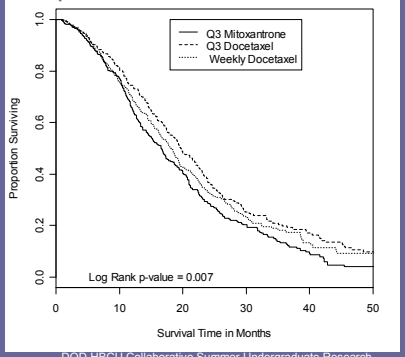
How do we 'treat" the data?



Set of tools for time-to-event outcomes

- "Survival analysis"
- Kaplan-Meier curves: graphical representation
- Kaplan-Meier estimation: provides point estimates and confidence intervals
- Logrank test: tests for differences across groups

Kaplan-Meier curves



Summary

- Biostatisticians have a lot of tools for helping with prostate cancer research
- Critical areas of assistance:
  - study design
  - sample size estimation
  - data analysis
- Prostate cancer has some specific areas that make it challenging
  - measurement issues with standard outcomes
  - time to event outcomes require special methods

Prostatic Cancer Screening Controversies

Jonathan C. Picard, M.D.
Assistant Professor of Urology

Introduction

- Prostate Cancer
  - Most common noncutaneous cancer in men in the US
  - Second leading cause of death in men in the US (estimated 28,660 deaths in 2008)
    - Jemal 2008
  - In a recent analysis of organ donors, prostate cancer was incidentally found in approximately one-third of men aged 60-69 and 46% of men over age 70
    - Yin 2008
  - The lifetime risk of prostate cancer death is only 3%
    - Ries 2008

Introduction

- Prostate Cancer Screening

Who should be screened?

How often should the screening be performed?

What is the PSA threshold that triggers further testing?

Introduction

- PSA is a glycoprotein produced by the epithelial cells that line the acini and ducts of the prostate gland.
- Exists in two forms: protein-bound and free
- The choice of PSA threshold above which one should undergo further evaluation is controversial

Introduction

- Multiple causes of elevated PSA levels
  - Benign prostatic hyperplasia (BPH)
  - Prostatitis
  - Prostate trauma
  - Prostate cancer

Where do we stand?

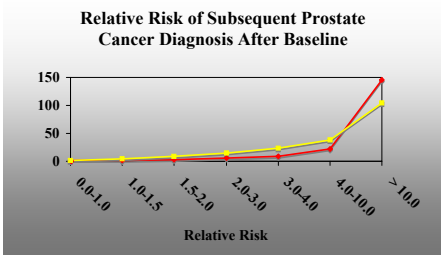
- AUA Screening Guidelines
  - PSA and DRE annually beginning at age 40
    - African American Men
    - Men with family history of prostate cancer
  - PSA and DRE annually beginning at age 50
- ACS and NCCN recommend PSA and DRE annually for all men beginning at age 50
- Prostate cancer mortality in the US declined by approximately 30% between 1994 and 2005
  - Ries 2008

Who?

- Family History
  - Father or brother > 60 yrs (RR=2, AR=15%)
  - Father or brother < 60 yrs (RR=3, AR=20%)
  - Father AND brother (RR=4, AR=30%)
- Race
  - African Americans
    - Lifetime risk of disease (20.6%) vs whites (17.6%)
    - Lifetime risk of death from PCa (4.7%) vs whites (2.8%)
- Genetic Factors

Who?

- "Elevated" Baseline PSA

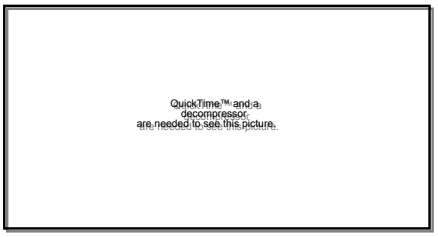


Antenor JA et al., J Urol 2004; 172:90.

How often?

- European Randomized Study of Screening for Prostate Cancer (ERSPC)
  - Suggests that most cancers detected 2-4 years after an initial screen will be curable.
    - Schroder 2009

What should be the PSA threshold?



Considerations

- European Randomized Study of Screening for Prostate Cancer (ERSPC)
  - 20% relative reduction in prostate cancer deaths among those screened when compared to those not screened at 9 years
  - 1410 men would not to be screened and 48 men treated for prevention of 1 prostate cancer death over 10 years
    - Schroder 2009

Considerations

- Prostate, Lung, Colon, and Ovary Trial (PLCO)
  - No difference in prostate cancer deaths at 7-10 years of follow-up when comparing those screened to unscreened
  - Many men in the study had previously undergone PSA testing prior to trial entry
  - Follow-up time may be insufficient to detect differences between cohorts
    - Andriole 2009

Improving PSA Testing

- PSA testing in pts with a PSA > 4 ng/mL has a sensitivity of 20%
  - Thompson 2005
- Age-specific PSA Ranges

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Improving PSA Testing

- PSA Kinetics (Doubling Time, Velocity)

PSA level-dependent

- PSA 0-4 => rise greater than 0.4 ng/mL per year
  - Moul 2007
- PSA 4-10 => rise greater than 0.75 ng/mL per year
  - Carter 1992

Age-dependent

- Age 40-59 => rise greater than 0.25 ng/mL per year
- Age 60-69 => rise greater than 0.5 ng/mL per year
- Age > 70 => rise greater than 0.75 ng/mL per year
  - Moul 2007

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Improving PSA Testing

- Percent Free PSA
  - Provides a modest benefit when the following conditions are met:
    - PSA 4-10 ng/mL
    - Percent PSA is less than 7-10% => indicates high risk of prostate cancer
    - Percent PSA is greater than 20-25% => indicates a low risk of prostate cancer
- PSA Density
  - Requires transrectal ultrasound volume assessment and highly dependent upon operator

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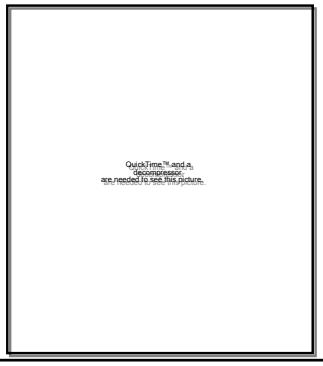
AUA Guidelines



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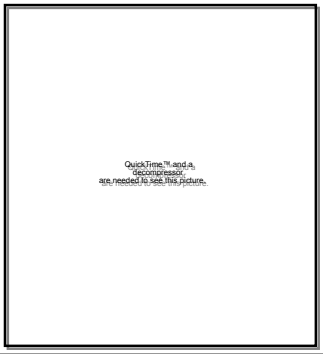
ACS Guidelines



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Summary

- PSA testing should be **offered** to all men over age 40 with at least a 10 year life expectancy
- Extensive discussion regarding the risks and benefits of testing and subsequent therapies should be performed
- Screening interval recommendation is not provided; however, one suggested approach would be biennial screening for men with PSA < 2 and annual screening for men with PSA of 2 or above.
- Consideration should be given to family history, race, prior history of PSA results and prostate biopsies

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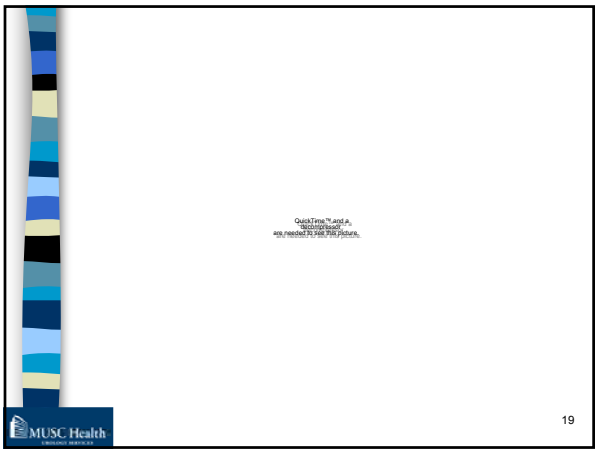
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TIFF (Uncompressed)
are needed to see this picture.
MUSC Health

19

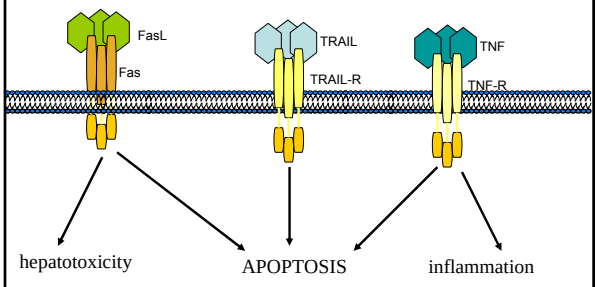
Enhancing Prostate Cancer Gene Delivery

Christina Voelkel-Johnson, Ph.D.
Department of Microbiology & Immunology
Cancer Immunology & Immunotherapy

Prostate Cancer

- 186,320 new cases (2008)
- 28,660 deaths (2008)
- 85% localized at diagnosis
- Slow growing, 5yr survival > 90%
- AA>caucasian>hispanic>asian>NA
- Mortality in AA=75%
- 1/6 males affected
- Treatment
  - Localized: radiation, surgery, watchful waiting
  - Advanced: hormone ablation (cancer becomes refractory)
  - Metastatic: chemotherapy (not curative, palliative)

Death Ligands as Cancer Therapeutics



TRAIL

(TNF Related Apoptosis Inducing Ligand /Apo2L)

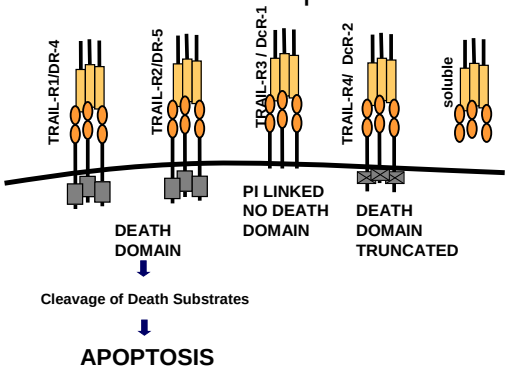
- discovered by 2 groups (Genentech/Immunex) 1995/1996
- member of the TNF superfamily (highest homology to FasL)
- Induces apoptosis in a variety of cancer cell lines
- Does not induce apoptosis in normal cells
- Preclinical studies confirmed safety of single agent therapy
- Clinical trials with rTRAIL and agonistic Ab against receptors ongoing

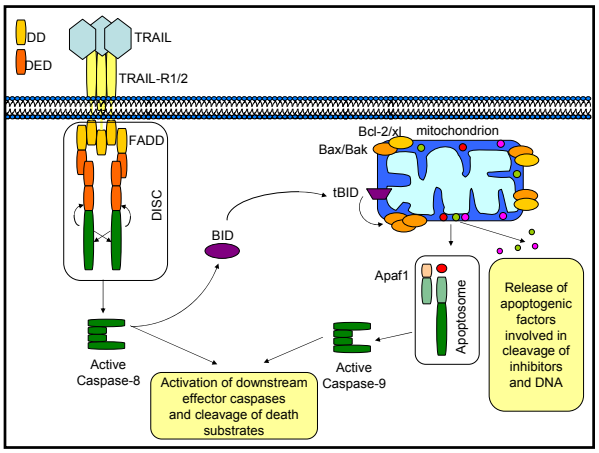
TRAIL

(TNF Related Apoptosis Inducing Ligand /Apo2L)

- TRAIL is expressed on a variety of activated immune cells
- TRAIL knockout mice are more susceptible to carcinogen-induced tumors
- Aging TRAIL knockout mice develop tumors of hematopoietic origin more frequently than controls
- BCG immunotherapy induces TRAIL release from neutrophils-correlates with treatment response

TRAIL Receptors





Status of TRAIL therapy

- Preclinical studies
  - Human tumor xenografts in mice (efficacy)
  - Non-human primates (safety)
- Clinical trials
  - Phase 1A: 39 patients, no response, no adverse effects
  - Phase 1A: 31 patients, 1PR, 5 SD, no adverse effects
  - Phase 1: 51 patients, 1 PR, 13 SD, adverse effects included fatigue, headache, fever, vomiting,nausea, anemia,weightloss
  - pharmacokinetic assessment in 37 patients with 0.5-15 mg/kg rTRAIL revealed that serum concentration similar to xenograft studies can be safely achieved in humans.

Issue: short half-life of rTRAIL in circulation

(Suicide) Gene Therapy

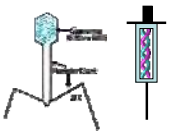
- Gene therapy is a technique for correcting defective genes responsible for disease development
- Suicide gene therapy involves a gene that when expressed leads to death of the infected cell
- The most common vector is a virus, since viruses have naturally evolved to infect human cells and deliver their genetic material
- Scientists manipulate the virus and insert a gene of interest to correct disease

http://www.ornl.gov/sci/techresources/Human_Genome/medicine/genetherapy.shtml

Infectious Viruses: A Genetic "Syringe"

Viruses are composed of genetic material encapsulated in a protein coat.

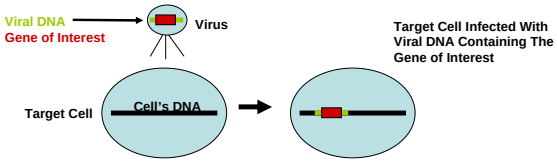
Viruses inject their genetic material into target cells.



DNA Loaded Syringe

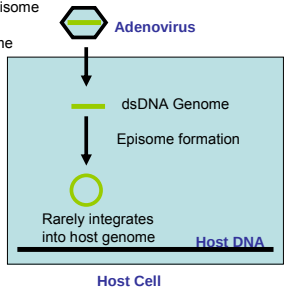
Viruses infect target cells with their genetic material.

The viral DNA can be altered to contain a gene of interest (rDNA) to infect that gene into the target cell.



Adenovirus

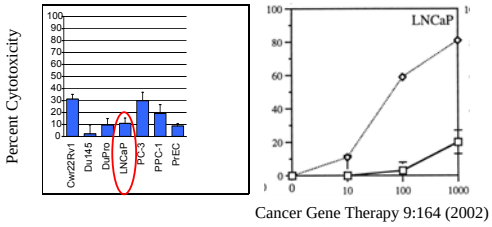
- dsDNA genome
- Non-Lipid Enveloped
- Upon infection, the viral DNA forms an episome
- Episome rarely integrates into host genome
- Fixed host range affecting Rodents, humans and other animals
- Known receptors: Coxsackie & Adenovirus Receptor (CAR) HLA / MHC I



Gene Therapy using TRAIL

- Full-length TRAIL (membrane bound form)
- IRES allows translation of two proteins from one mRNA
- GFP as marker for infected cells

AdTRAIL can kill cells resistant to rTRAIL



Cancer Gene Therapy 9:164 (2002)

Wouldn't it be great if….

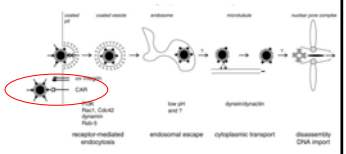
…we could inject prostate cancer patients with AdTRAIL to kill the cancer cells?

Problems

- Entry of adenovirus
  - via receptor
- Tropism of adenovirus
  - Liver and lungs
- Neutralization by the immune system

Problems

Entry of adenovirus via receptor



CAR - originally discovered as a viral receptor but later found to be an adhesion molecule

Do cancer cells adhere?

Problems

Do cancer cells adhere?

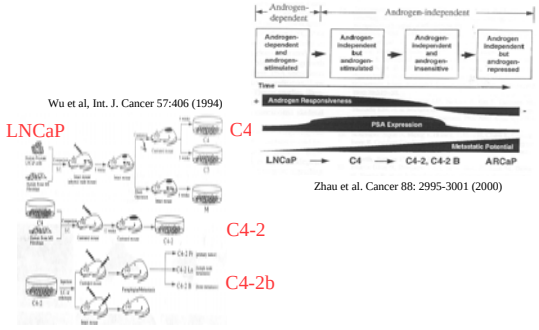
Downregulation of adhesion proteins is a prerequisite for the ability to metastasize

CAR decreases in prostate cancer with increasing tumor stage and grade

Questions

1. Is there a model that simulates this decrease in CAR?
2. Can we use this model to test how CAR expression affects adenoviral entry?
3. What can be done to increase adenoviral entry?

The LNCaP progression model of PC



Wu et al, Int. J. Cancer 57:406 (1994)

Zhau et al. Cancer 88: 2995-3001 (2000)

LNCaP

C4

C4-2

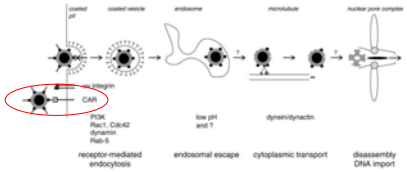
C4-2b

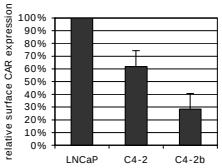
Flow cytometry

- Expression of proteins on the cell surface
  - Here: How much CAR is on LNCaP vs. C4-2b?
- Expression of reporter proteins
  - Here: we used GFP as a reporter to determine how many cells are infected by the adenovirus and how much of the transgene is expressed

probes.invitrogen.com/resources/.../tutorials/...Flow/player.html -

Adenoviral entry and CAR





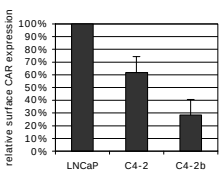
Questions

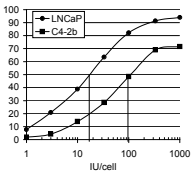
Is there a model that simulates this decrease in CAR? YES

Can we use this model to test how CAR expression affects adenoviral entry?

What can be done to increase adenoviral entry?

Adenoviral entry and CAR





Questions

Is there a model that simulates this decrease in CAR? YES

Can we use this model to test how CAR expression affects adenoviral entry? YES

What can be done to increase adenoviral entry?

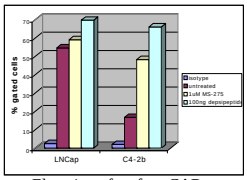
CAR and HDACi

- a novel class of chemotherapeutic drugs called histone deacetylase inhibitors (HDACi)

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

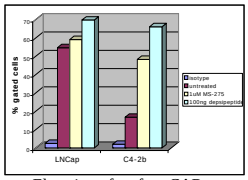
- In clinical trial for prostate cancer
- Increase CAR expression in bladder cancer
- Can HDACi increase CAR expression in prostate cancer cells?

HDACi restore CAR

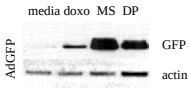


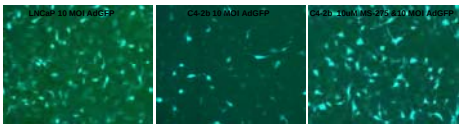
Elevation of surface CAR

HDACi increase infectivity



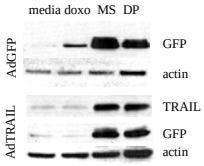
Elevation of surface CAR

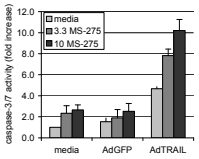




Increased adenoviral infectivity and gene expression

HDACi increases efficacy of AdTRAIL





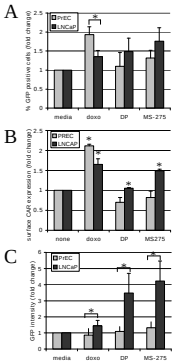
Increased efficacy of AdTRAIL

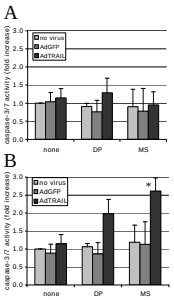
Conclusions-part 1

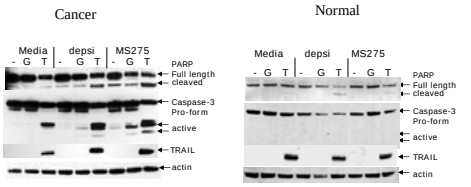
- AdTRAIL is more effective than rTRAIL
- Decreased expression of the adenoviral receptor CAR impairs adenoviral gene delivery
- HDACi restore CAR expression, increase adenoviral infectivity and gene expression, and improve efficacy in vitro

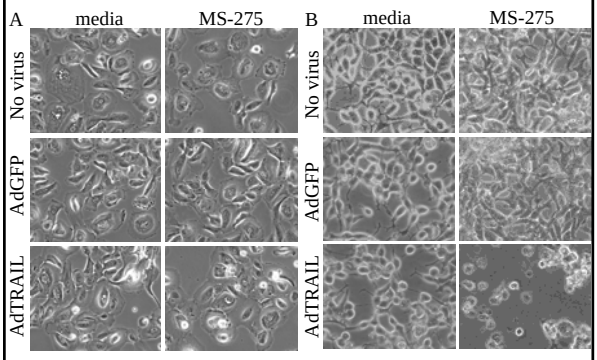
Selectivity

- The goal of any cancer therapy is to selectively kill tumor cells
- HDACi can be safely administered to cancer patients with lower side effects than other drugs
- Can HDACi increase adenoviral infection selectively in tumor cells?









Conclusions

- AdTRAIL is more effective than rTRAIL
- Decreased expression of the adenoviral receptor CAR impairs adenoviral gene delivery
- HDACi SELECTIVELY restore CAR expression, increase adenoviral infectivity and gene expression, and improve efficacy in vitro

What's next?

- Entry of adenovirus
  - via receptor
- Tropism of adenovirus
  - Liver and lungs
- Neutralization by the immune system

Employing Qualitative Methods in Research

Dr. Gayenell S. Magwood
Assistant Professor
July 2009

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Objectives

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Qualitative Research

"A systematic interactive approach used to describe and give meaning to life experiences."

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Qualitative Research

"Interpetivisim, or the qual approach, is a way to gain insight through discovering meanings by improving our comprehension of the whole…." (Strauss & Corbin)

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Beliefs and Assumptions

Are based on:

- The nature of reality
- The relationship of the knower to the known
- The possibility of generalization
- The possibility of causal linkages
- The role of values

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Beliefs and Assumptions

Quantitative

- Reality is single, tangible, and fragmentable
- Knower and known are independent
- Time- and context-free generalizations are possible

Qualitative

- Realities are multiple, constructed, and holistic
- Knower and known are interactive, inseparable
- Only time- and context-bound working hypotheses are possible

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Lincoln & Guba 1985

Beliefs and Assumptions

Quantitative

- There are real causes, temporally precedent to or simultaneous with their effects
- Inquiry is value-free

Qualitative

- All entities are in a state of mutual simultaneous shaping…impossible to distinguish cause from effects
- Inquiry is value-bound

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Lincoln & Guba 1985

Qualitative Research

- Non-numerical and non-inferential
- Natural settings with contexts part of the phenomenon
- Differing world views
- Involvement of the researcher
- Descriptions, observations, and accounts of participants, rather than 'subject'

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Qualitative Research

- Process
- Meaning
- Primary instrument
- Fieldwork
- Descriptive
- Inductive

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Quantitative and Qualitative Inquiry

Quantitative

- Assumptions
  - Etic
  - Variables identified and relations measured
  - Method
  - Social facts have objective reality

Qualitative

- Assumptions
  - Emic
  - Variables are complex, interconnected, and difficult to measure
  - Subject matter (the phenomenon)
  - Reality is socially constructed

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Quantitative and Qualitative Inquiry

Quantitative

- Purpose
  - Generalizability
  - Prediction
  - Explanations of Causation
- Researcher Role
  - _____
  - _____

Qualitative

- Purpose
  - Contextualization
  - Interpretation
  - Understanding perspectives
- Researcher Role
  - _____
  - _____

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Quantitative and Qualitative Inquiry

Quantitative

- Approach
  - Begins with hypotheses and theories
  - Manipulation and control
  - Instruments*
  - Experimentation
  - Deductive
  - Consensus
  - Reduces data to numerical indices
  - Abstract language in write-up*

Qualitative

- Approach
  - Ends with hypotheses and grounded theory
  - Emergence and portrayal
  - Instruments*
  - Naturalistic
  - Inductive
  - Searches for patterns
  - Pluralism, complexity
  - Minor use of numerical data
  - Descriptive write-up*

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Qualitative --Quantitative

Informants

1. What do informants know about their culture [disease] that I can discover?
2. What concepts do informants use to classify their experiences?
3. How do informants define these concepts?

Subjects

1. What do I know about a problem that will allow me to formulate and test a hypothesis?
2. What concepts can I use to test this hypothesis?
3. How can I operationally define these concepts?

Spradley (1979)

Qualitative --Quantitative

Informants

4. What folk theory do informants use to explain their experiences?
5. How can I translate the cultural knowledge of my informants into a cultural (or context based) description that peers will understand?

Subjects

4. What scientific theory can explain the data?
5. How can I interpret the results and report them in the language of my peers?

Spradley (1979)

Variations in Methodology

- Ethnography (including field research & participant observation)
- Grounded theory
- Phenomenology
- Case Study
- Historical (includes oral history)
- Narrative analysis

Data Collection Methods

- One to one qualitative interviews (open-ended questions)
- Interactive questioning & the creation of accounts (using elicitation devices)
- Focus groups
- Observations & video recording
- Written texts from participants or records (includes onlines sources)

DATA ANALYSIS

- Typology
- Taxonomy
- Constant Comparative
- Analytic Induction
- Matrix Analysis/Logical Analysis
- Quasi-statistics
- Microanalysis
- Metaphorical Analysis
- Domain
- Hermeneutical
- Discourse Analysis
- Semiotics
- Content
- Heuristic Analysis
- Narrative

Mixed Methods

- *Triangulation*- test for consistency of findings through different instruments
- *Complementarity*- clarifies and illustrates results from one method with the use of another method
- *Development*- results from one method shape subsequent methods or steps in the research process
- *Initiation*- new research questions or challenges results
- *Expansion*- provides details and richness

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Green et al. (1989)

What do you want to know?

- How
- When
- Where
- Who

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EXAMPLE

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Methodological Challenges with Coding in Qualitative Research

Charlene Pope, PhD, MPH

Gayenell Magwood, PhD, MSN

Catherine Ling, MSN, BSN, BA

Boyd Davis, PhD

MUSC MEDICAL UNIVERSITY OF SOUTH CAROLINA COLLEGE OF NURSING

Objectives

- **REVIEW OF QUALITATIVE PROJECT :**
- **INTENT: Compare open-coding from grounded theory with narrative process coding and situational analysis for social context cues**
- **OUTCOME: Contrast the results of variations in qualitative coding with linguistic stance analysis (quantitative) as a means of triangulation to determine impact on disparities research**

Why compare coding for Diabetes Disparities Research?

- ***Need for social contexts to contribute to a community-based intervention***
- ***To produce culturally tailored interventions***
- ***Consider if race matters when coding***

- **PARENT QUALITATIVE STUDY: Identify the beliefs, attitudes, experiences, and practices that contribute to avoidable ER visits for African Americans with diabetes [REACH 2010, NIH-NINR, MUSC]**

Diabetes Self-Management

Studies:

- **Under-represent Black people**
- **Often omit racial/ethnic identification**
- **Rarely culturally tailor interventions**
- **Show few significant differences**
- **Often exclude social, cultural, and environmental contexts**

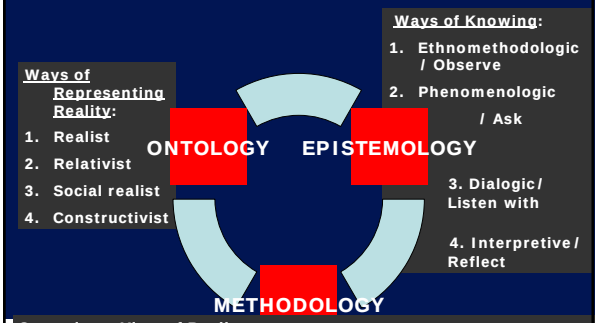
Qualitative Research in Diabetes with African Americans

- **"Focus Groups" or "Interviews" =**

  Only research design classification
- **Interviews often structured, organized by investigator framework, or semi-structured with an agenda (Limitations)**
- **Coding = Usually software designated; least described component of studies**

  Themes identified by team, content analysis (agenda-driven) or coding approach often not identified or described (Open-coding)

Approaches to Qualitative Research

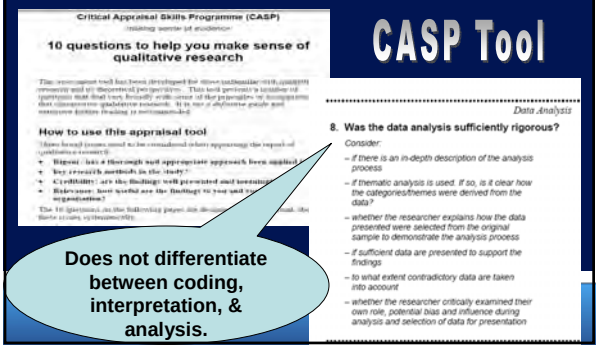


Capturing a View of Reality:

1. Interviews/groups
2. Transcriptions
3. Text analysis
4. Observations
5. Participation
6. Mixed methods

Critical Appraisal of Qualitative

http://www.phru.nhs.uk/Doc_Links/Qualitative%20Appraisal%20Tool.pdf



Does not differentiate between coding, interpretation, & analysis.

Quality Issues

- **Researcher identity**
- **Entry into the setting**
- **Participant access and trust**
- **Sample identification**
- **Data recording and management**
- **Transcription (what/how much) and coding**
- **Logic trail of decision making**
- **Interpretation**
- **Analysis (Refrain from leaping beyond data)**

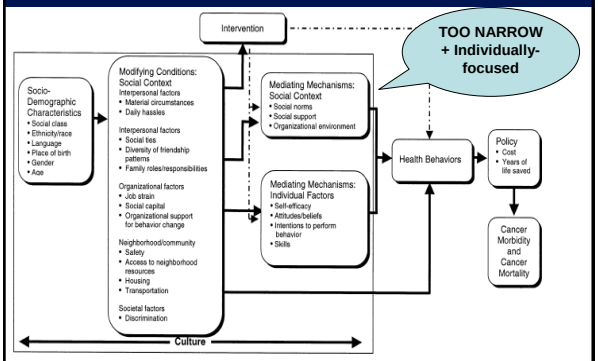
Where do codes come from?

38 qualitative studies regarding Diabetes with Black populations

- **Does a coding approach matter?**

RESEARCH QUESTION: Does the application of one coding approach produce more cues of social context than another?

Defining Social Contexts



Ref: Sorensen, G, et al. (2003). Model for incorporating social context in health behavior interventions. *Preventive Medicine, 37,* 188-197.

Example of Social Context Themes for African Americans with Diabetes

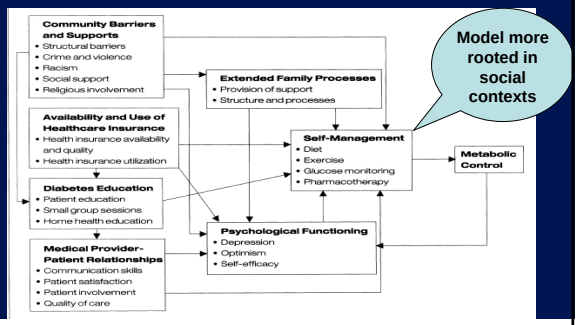
- Spirituality
- Diabetes impact on life
- Multi-caregiver roles
- Stress
- Coping styles
- Social support

Predominantly Psychosocial

No mention of insurance, SES, structures, environment, providers, discrimination, health system, material resources for disease

Ref: Samuel-Hodge, C. et al. (2000). Influences on day-to-day self-management of Type 2 diabetes among African American women. *Diabetes Care, 23,* 928-933.

Social Contexts in Diabetes Self-Management



Brody, G. et al. (2001). Heuristic model linking contextual processes in African American adults with Type 2 diabetes. *Diabetes Educator, 27, 685-693.*

Research Design

- 6 qualitative semi-structured interviews collected with a grounded theory design
- Sample: Black patients with diabetes who were seen for an avoidable ER visit
- First, open-coding in Strauss & Corbin tradition
- Second, narrative process coding (Angus)
- Third, situational analysis (Clarke)
- Triangulation: Quantitative computerized stance analysis (Mason & Davis)

Open Coding

- Starts with Grounded Theory assumptions: Preconception limits & interview descriptions
- More than interviews (observations, field notes, memos, concept maps, etc.)
- Concepts from the Text vs Content in the Text
- Patterns, conditions, properties, action, constant comparisons, categories, themes
- Axial and selective coding, combinations

Narrative Process Coding

- External narrative process (description of events: past, present, future)
- Internal narrative process (subjective or experiential description of experience; includes emotions and metaphors)
- Reflexive narrative process (interpretation, analysis or reflection on past, present, current events and significance or cues for behaviors)

Situational Analysis

- Situational maps (human, non-human, discursive and other elements & relations)
- Social worlds/arenas maps (collective actors, key non-human elements & commitments or negotiations
- Positional maps (positions taken and not taken regarding variations & differences in the data)

Stance and its Analysis

- Stance signals for evidentiality, evaluation, affect and agency occur throughout interaction
- Analysis performs corpus-based multivariate analysis of two dozen language features associated with affect, agency, evaluation and intention in successive standardized sections
- Software identifies, tabulates features, and scales significant sections where stance changes; researcher can then interpret

Ref: Davis, B. & Mason, P. 2007 i.p., Locating presence and position in online focus group chat. In St.Amant & Sidley, eds., *Handbook of Research in Computer-Mediated Communication*. Hershey: Idea Press

Analysis: Comparative Coding

- Four coders, one for each method
- Contrasts of common codes using the 2 frameworks of social contexts
- Interpretation

Open-Coding

- Administrative Factors
- Desired / Absent Services
- Provider Interaction
- Knowledge Deficits
- Barriers / Negative Impactors
- Current Services
- Emergent Care
- Diabetes as Entity
- Life Choices
- Unknown

Open Coding Examples

Demographics, etc	Admin
listening	Desired/Absent Services
disinterested	Provider Interaction
chastizing	Provider Interaction
food choice	Life Choices
depression	Barrier/Negative Impactor
confusion	Current Services
financial	Barrier/Negative Impactor
physical activity	Life Choices
Services	Desired/Absent Services
guarding	Provider Interaction
distrust	Provider Interaction
Killer	Diabetes as entity

Axial Coding Examples

Prevailing Themes Across Coding

- Constitution of Diabetes as unnamed external entity: *"It" (Not Owned)*
- Deficits in provider-patient communication
- Emotional Distress: Fears, too proud to ask help, mistrust of health system, depression
- Denies seriousness as symptoms escalate

Variations: Narrative Process

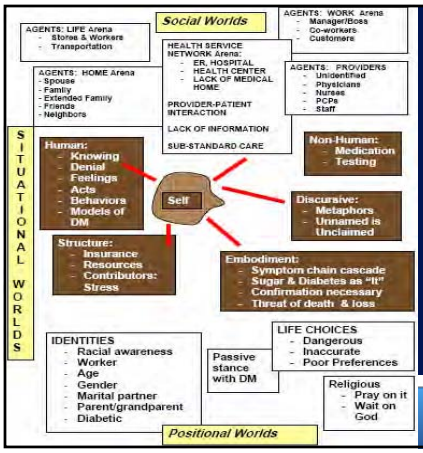
- External Processes
  - Trigger events (stress)
  - Detailed lists of regimens, hints of trying to convince
- Internal Processes
  - Burden to self & others
  - Overwhelmed Roles
  - Economic discrimination
  - Self-blame
  - Metaphors
    - Roller Coaster
- Reflective
  - Denies seriousness
  - Uncertainty
  - Guilt, FEAR
  - Non-healthful behaviors

Examples

- "Could be worse"
- *"There are people worse off"*
- *"I don't let it worry me"* – belief in God
- Depression: *"Sometime down, up and down"*
- *"I would say I know a pretty good bit about diabetes…but I know I don't know all I need to know"*

Variations: Situational Analysis

- Access barriers: job changes, insurance, provider refusals, lack of explanations, reception
- Subordinate role in ER decisions to family, friends and coworkers
- Lack or loss of control, fear of effect on public behavior/harm to others
- Sources of DM knowing: relatives, media, those who know others with DM
- Threats: death, amputation
- Awareness of race & racial disparities



Messy Map of Life with Diabetes

Examples: Social Contexts

- Escalating symptom chain without action
- Contribution of work site & co-workers
- Strategies of denial (*close my eyes & shake it off*) shared in family networks
- Unnamed 'it' as external attacker, not owned or claimed as a cultural model of DM in SC
- Uneven knowledge of self-management, tied to patient-provider interactions, lack of medical home, uninsured or changing insurance status, care without sufficient explanations
- Collective decisions with family

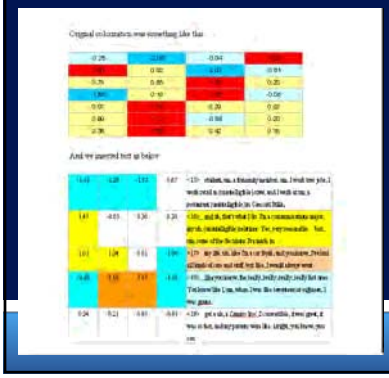
Stance Analysis

- **6 metaphors for living with diabetes (most of all coding approaches)**
- **What speakers do not consciously realize is that their words fall into patterns, and those patterns can be measured to discover underlying attitudes and emotions: their *stance*.**
- ***People are generally unaware that their stance is showing***

Stance Analysis

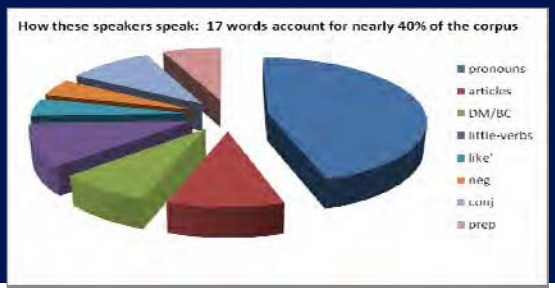
- **Factor analysis of 24 language feature categories (such as pronouns, modal verbs, negations, etc.).**
- **From that analysis, 4 factors that characterize different dimensions of stance were identified (Mason et al. 2005). We scale those factors as:**
- **Scale 1 signals a speaker's opinion, and the weight s/he gives to it**
- **Scale 2 presents the rationale behind the opinion**
- **Scale 3 shows how the speaker uses details to show the strength of feelings**
- **Scale 4 shows the speaker's personalization or ownership or assigning of action**

Coding with Stance Analysis

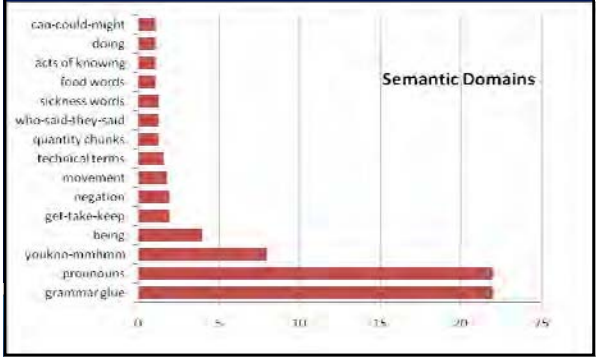


- **The identification of hot spots in social interaction with factor analysis**

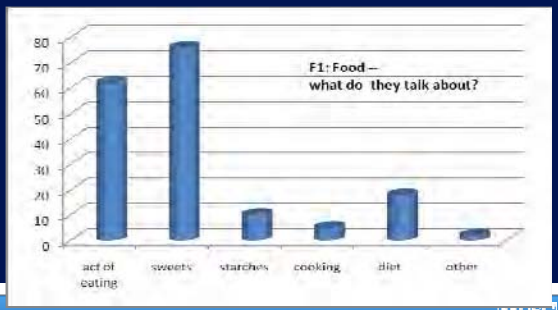
Linguistic Assessment



Determining When Stance Shifts



Where Food Attention Lies



Thematic Clusters in Stance Analysis

- **Personalization (viewing the disease as 'It' & outside me**
- **Rationale for ER Visits: Usually tied to symptoms & other people, but not causes or self-made decisions**
- **Feelings/Details/Elaboration:**
  - **Re-visiting Sugarland**
  - **Safety Net with holes (Providers)**

Implications for Intervention

- **Reduction of observer bias with stance analysis**
- **Increased social context cues with situational analysis parallel stance analysis & suggest interventions**
- **Stance analysis identified 10 questions for ranking in tool to improve provider-patient interviewing**

Questions for Investigators:

- ***Are there potential consequences to variations in coding?***
- ***Does the race of investigators matter in qualitative coding and analysis?***
- ***Why is there so little reflexivity about coding?***
- ***What adjustments should be made?***

Limitations of the Comparison

- **Nature of the semi-structured interview**
- **Similarities of the coders perspectives**
- **Did not compare notes until separate coding finished**

Conclusion

- **Coding of qualitative data is the least transparent, most poorly described component of qualitative studies**
- **Coding matters**
- **Approaches that do not seek social contexts do not find them as readily**

The (long, but fulfilling) Journey to a Dual-Degree

Gabrielle F. Cannick, DMD, PhD

July 7, 2009

Gabrielle's Timeline 2001-2009

Or:

What I did for the last 8 years at MUSC

2001-2002
First Year of Dental School

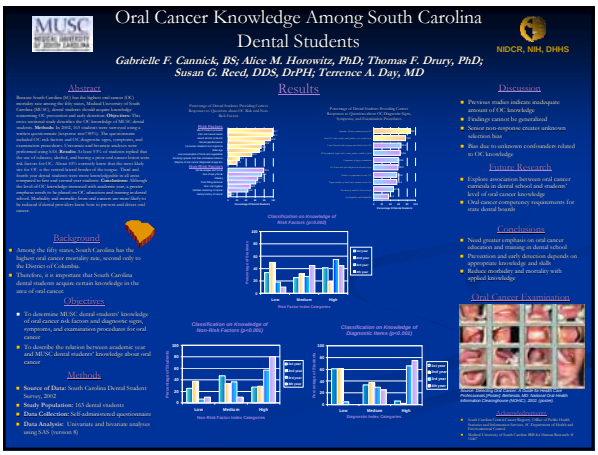
2002-2003
Got Married
Started Grad School

2003-2004
NIDCR/NIH

Oral Cancer Knowledge Among South Carolina Dental Students

Gabrielle F. Cannick, BS; Alice M. Horowitz, PhD; Thomas F. Drury, PhD; Susan G. Reed, DDS, DrPH; Terrence A. Day, MD

NIDCR, NIH, DHHS



1

2004-2006
Dissertation/Life


2006-2007
Returned to Dental School

2007-2009
Family/Dental School


2009
I'm finally done!

Drs. Sparkle Pompey and Gabrielle Cannick

We're so glad to be finished!

Awards, Presentations, and Publications

Awards

Individual Predoctoral Dentist Scientist Fellowship, NIDCR F30DE017046 (2005-2009)

APHA Anthony Westwater Jong Memorial Community Dental Public Health Pre-professional Award(2006)

Presentations

Cannick, GF, AM Horowitz, DR Garr, BW Neville, SG Reed, RF Woolson, TA Day, and DT Lackland. **Use of PRECEDE-PROCEED to develop an oral cancer prevention and detection curriculum.** Second North American Congress of Epidemiology, Seattle. June 21-24, 2006. Poster Presentation.

Cannick, GF, AM Horowitz, DR Garr, BW Neville, SG Reed, TA Day, and DT Lackland. **A model for change: oral cancer in the dental school curriculum.** National Oral Health Conference, Little Rock. May 1-3, 2006. Roundtable Presentation.

Cannick, GF. **Development and implementation of an oral cancer educational program for dental students.** American Public Health Association 133rd Annual Meeting, Philadelphia. December 10-14, 2005. Invited Oral Presentation.

Cannick, GF and DT Lackland. **Development and implementation of an oral cancer educational program for dental students.** Medical University of South Carolina Student Research Day, Charleston. November 4, 2005. Poster Presentation

Publications

Cannick, G.F.1,2, A.M. Horowitz2, T.F. Drury2, S.G. Reed3, T. A. Day4, 1Department of Biometry and Epidemiology, College of Graduate Studies, and College of Dental Medicine, Medical University of South Carolina (MUSC), 2 National Institute of Dental and Craniofacial Research, National Institutes of Health; 3 Department of Stomatology, College of Dental Medicine, MUSC; 4 Department of Otolaryngology- Head and Neck Surgery, MUSC. **Assessing oral cancer knowledge among dental students in South Carolina.** Journal of the American Dental Association. 2005;136:373-8.

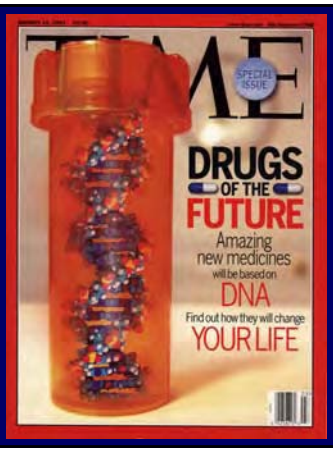
Cannick, G.F-1, A.M. Horowitz2, S.G. Reed1, T.F. Drury2, T.A. Day3,1Department of Stomatology and Department of Biostatistics, Bioinformatics, and Epidemiology, Medical University of South Carolina (MUSC),2National Institute of Dental and Craniofacial Research, National Institutes of Health;3Department of Otolaryngology-Head and Neck Surgery, MUSC. **Opinions of South Carolina Dental Students toward Tobacco Use Interventions.** Journal of Public Health Dentistry. 2006;66(1):44-8.

Cannick GF, Horowitz AM, Garr DR, Reed SG, Neville BW, Day TA, Woolson RF, Lackland DT. Oral Cancer Prevention and Early Detection: Using the PRECEDE–PROCEED framework to guide the training of health professional students. Journal of Cancer Education 2007;22(4):250-3.

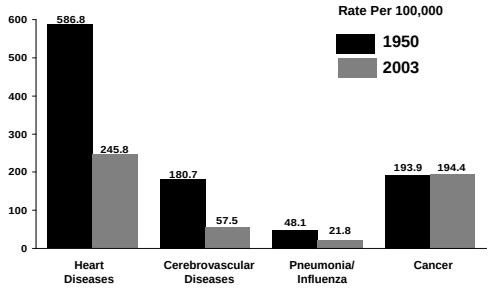
Cannick GF, Horowitz AM, Garr DR, Reed SG, Neville BW, Day TA, Woolson RF, Lackland DT. Use of the OSCE to evaluate brief communication skills training for dental students. Journal of Dental Education 2007;71(9):1203-9.

GENE THERAPY: UPDATE AND FUTURE PROMISE

James S Norris PhD
Professor and Chairman
Dept of Microbiology and Immunology
Medical University of SC



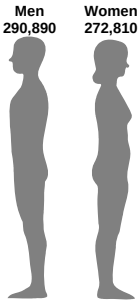
Change in the US Death Rates* by Cause (1950 & 2003)



* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2001 Mortality Data–NVSR-Death Final Data 2001–Volume 52, No. 3.
http://www.cdc.gov/nchs/data/nvsr/nvsr52/nvsr52_03.pdf

2004 Estimated US Cancer Deaths*

Lung & bronchus	32%
Prostate	10%
Colon & rectum	10%
Pancreas	5%
Leukemia	5%
Non-Hodgkin lymphoma	4%
Esophagus	4%
Liver & intrahepatic bile duct	3%
Urinary bladder	3%
Kidney	3%
All other sites	21%



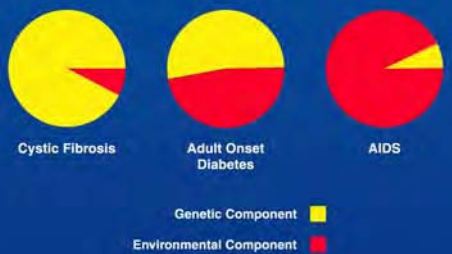
- •25% Lung & bronchus
- •15% Breast
- •10% Colon & rectum
- • 6% Ovary
- • 6% Pancreas
- • 4% Leukemia
- • 3% Non-Hodgkin lymphoma
- • 3% Uterine corpus
- • 2% Multiple myeloma
- • 2% Brain/ONS
- •24% All other sites

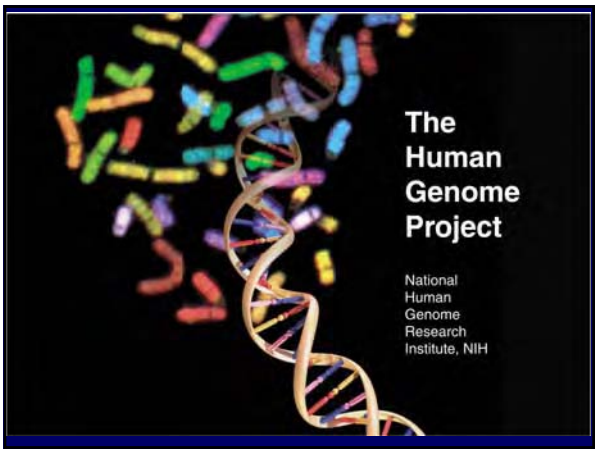
ONS=Other nervous system.
Source: American Cancer Society, 2004.

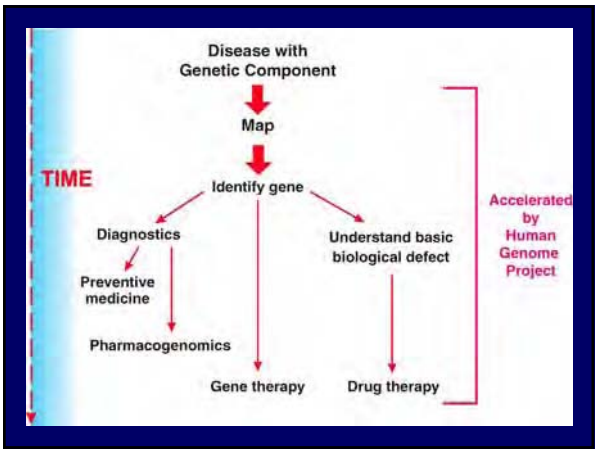
There are no perfect genetic specimens

All of us carry an estimated 5- 50 significant gene flaws

Virtually All Diseases (Except Maybe Trauma) Have a Genetic Component







Applications of Genetic Tests

- Confirm a suspected clinical diagnosis
- Detect a carrier for a recessive disease
- Prenatal diagnosis
- Newborn screening
- Susceptibility testing for a healthy individual
- Prediction of responsiveness to therapy

Ethical, Legal, and Social Implications

An integral component of the Human Genome Project

Will effective legislative solutions to genetic discrimination be found?

Will we successfully shepherd new genetic tests from research into clinical practice?

Can health care providers and the public become genetically literate in time?

Will the benefits of the advances in genetics only be available to a privileged few?

Will we arrive at consensus about the limits of genetic technology for trait enhancement?

2010

- Predictive genetic tests available for a dozen conditions
- Interventions to reduce risk available for several of these
- Many primary care providers begin to practice genetic medicine
- Pre-implantation diagnosis widely available, limits being fiercely debated
- Reasonably effective federal legislative solutions to genetic discrimination and privacy in place in US
- Access remains inequitable, especially in developing world

2020

- Gene-based designer drugs for diabetes, hypertension, etc., coming on the market
- Cancer therapy is precisely targeted to molecular fingerprint of tumor
- Dx/Rx pharmacogenomic approach is standard practice for many drugs
- Mental illness diagnosis transformed, new therapies under study, societal views shifting
- Homologous recombination technology suggests Germ line gene therapy could be safe

2030

- Comprehensive genomics- based health care is the norm
- Individualized preventive medicine available
- Environmental factors, and their interaction with genotype, pinpointed for many diseases
- Illnesses are detected early by molecular surveillance
- Gene therapy and gene- based drug therapy available for many diseases
- Full computer model of human cell replaces many laboratory experiments
- Average life span reaches 90 years, stressing prior socioeconomic norms
- Major anti- technology movements active in US, elsewhere
- Serious debate is underway about humans possibly “taking charge” of their own evolution

Gene therapy

Defined as the treatment or prevention of disease by gene transfer

First clinical trials began in 1990

Categories of gene therapy

1- Somatic gene therapy – Faulty genes are compensated for by inserting copies of a replacement gene into the affected tissue where the gene is expressed. To date, virtually all the research has been in this category.

Categories of gene therapy

2- Germ line gene therapy – Modifications of the human germ-line to replace disease alleles. Very controversial- can cause permanent changes to the gene pool.

Gene-transfer systems

Viral vectors

The virus still retains its capability to transfer its genetic material into host cells.

Gene-transfer systems

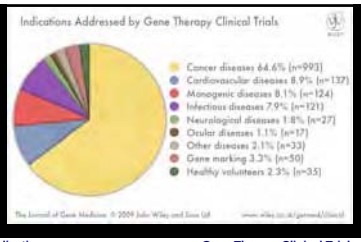
Viral vectors

Most viral vectors are derivatives of adenovirus – the virus associated with the common cold. In this approach, harmful genes are first deleted from the virus, making it pathogenically disabled. Therapeutic genes are then inserted into the viral DNA. Now replication competent viruses in use.

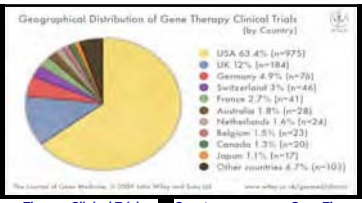
Gene-transfer systems

Retroviral vectors

As with viral vectors, harmful genes are first removed, before inserting the allele to be transferred.

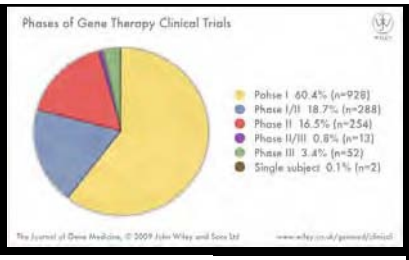


Indications	Gene Therapy Clinical Trials	
	#	%
Cancer diseases	993	64.6
Cardiovascular diseases	137	8.9
Gene marking	50	3.3
Healthy volunteers	35	2.3
Infectious diseases	121	7.9
Monogenic diseases	124	8.1
Neurological diseases	27	1.8
Ocular diseases	17	1.1
Others	33	2.1
Total	1537	

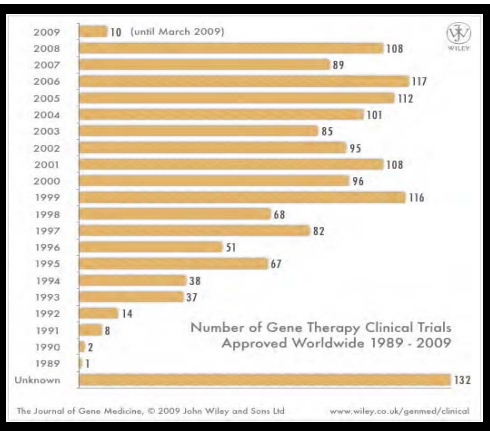


Country	Gene Therapy Clinical Trials	
	#	%
Australia	28	1.8
Austria	2	0.1
Belgium	23	1.5
Canada	20	1.3
China	12	0.8
Czech Republic	1	0.1
Denmark	2	0.1
Egypt	1	0.1
Finland	4	0.3
France	41	2.7
Germany	76	4.9
Israel	7	0.5
Italy	16	1
Japan	17	1.1
Mexico	1	0.1

Country	Gene Therapy Clinical Trials	
	#	%
Netherlands	24	1.6
New Zealand	2	0.1
Norway	4	0.3
Poland	6	0.4
Russia	1	0.1
Singapore	2	0.1
South Korea	13	0.8
Spain	9	0.6
Sweden	6	0.4
Switzerland	46	3
Taiwan	1	0.1
UK	184	12
USA	975	63.4
Multi-country	13	0.8
Total	1537	



Phase	Gene Therapy Clinical Trials	
	#	%
Phase I	928	60.4
Phase I/II	288	18.7
Phase II	254	16.5
Phase II/III	13	0.8
Phase III	52	3.4
Single subject	2	0.1
Total	1537	



Evaluation of Functional p53 Biomarker Profiles to Predict Efficacy of Adenoviral p53 Gene Therapy (Advexin) in Patients with Recurrent Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Slides courtesy of John J. Nemunaitis, M.D.

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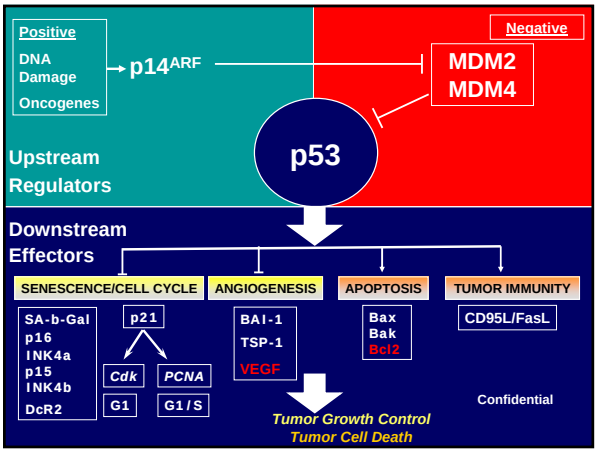
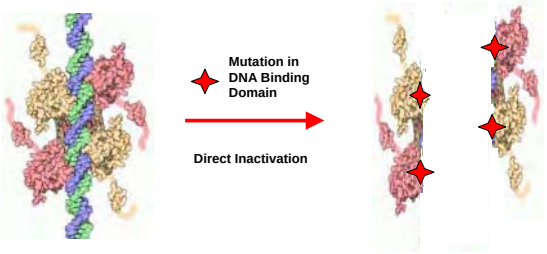


DNA binding domain mutations inactivate p53 by formation of tetramers that will not bind DNA

WT p53 Normal Tetramer Binds DNA

Mutant p53 tetramers are Inactive and Do Not Bind DNA



* > 80% of p53 mutations occur in the DNA binding domain

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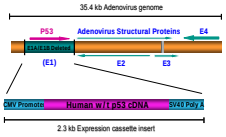
ADVEXIN® Adenoviral p53

- ADVEXIN is a, replication deficient, serotype 5 Adenovirus; the delivery system. ADVEXIN contains a p53 expression cassette in the deleted E1 region of the viral genome; the cleaning agent. Similar to Genedicine
- ADVEXIN is a non-enveloped, double stranded DNA virus, 100nm in diameter. It consists of an icosahedral particle with 20 triangular surfaces and 12 vertices. The delivery agent. It has proven very safe for man in over 600 trials.
- ADVEXIN injected into the tumor produces a transient (2-3 weeks) expression of the p53 trans-gene prior to being cleared from the body. ADVEXIN is a non-integrating DNA vector.



Representation of Adenovirus

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Confidential

ADVEXIN® was safe in >600 Treated Patients

Body System	EVENT	Serious Adverse Event
		%
Body as a Whole	Fever	1.3
	Pain	0.2
	Asthenia	0
	Infection local	0.5
	Tumor hemorrhage	0.6
	In patient Procedure	0
Digestive	Vomiting	0.2
	Dysphagia	0.2
Respiratory System		
	Pneumonia	0.8
	Dyspnea	0.6
	Apnea	0
CVS	Hypotension	0.2
	Heart arrest	0
Metabolic and Nutritional	Dehydration	0.6
	Kidney Failure	0.8

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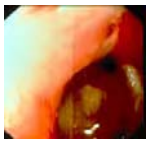
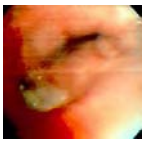
Objective Regression of Non-Small Cell Lung Cancer

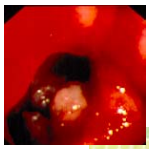
Day 0



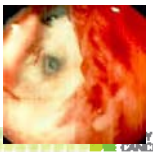
Day 3



Day 14



Day 28



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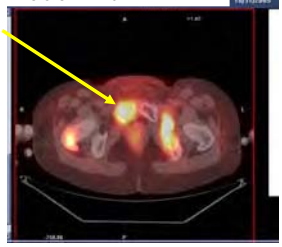
ADVEXIN® Therapy

Complete Response of Li-Fraumeni

Before Rx with ADVEXIN



After Rx with ADVEXIN

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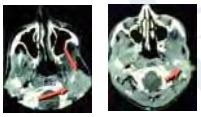
Advexin® Monotherapy in SCCHN Intra-Tumoral Administration and Clinical Response

Before Cycle 3

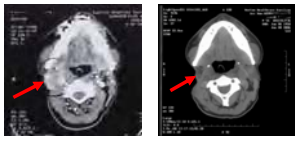
Response After ADVEXIN® Treatment (Monotherapy) in Head & Neck Cancer



Refractory to surgery, chemotherapy and radiation therapy

80% regression

ADVEXIN® Monotherapy in SCCHN Long Term Survivor Continues Monthly ADVEXIN® Treatments > 8 years



Baseline: 27 May 1998

CR: 8 June 2006

ADVEXIN® Head and Neck Cancer Clinical Trials

Trial	Phase	Number of Patients (Advexin)	Description
T301	Phase 3	123 (63)	Randomized Controlled Multicenter vs. Methotrexate
T201	Phase 2	112 (112)	Randomized Controlled Multicenter Dose Comparison
INT-002	Phase 1	7 (7)	Single Arm Single Institution Response Only

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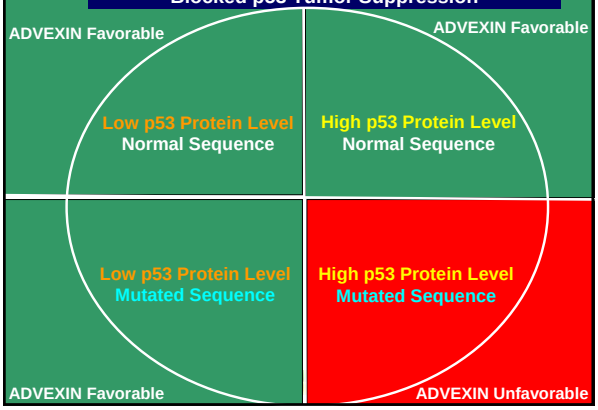
Patient Populations with Blocked p53 Tumor Suppression



p53 IHC/Sequence Profiles Favorable and Unfavorable for Advexin Efficacy Predict Tumor Growth Control in Recurrent SCCHN

INT-002, T201 and T301 Advexin Treated Patients with p53 Profile Data – Preliminary Analysis

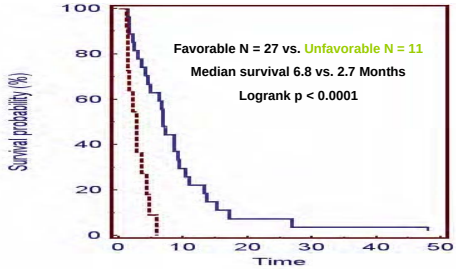
p53 Profile	Tumor Growth Control
Favorable	18/21 (86%)
Unfavorable	2/8 (25%)
Fisher's exact test p-value = 0.003	

Absolute Correlation between ≥ 10% Reduction in tumor size and favorable p53 biomarker profiles for Advexin efficacy

MARY CROWLEY CANCER RESEARCH CENTERS

p53 Profiles Favorable and Unfavorable for Advexin Efficacy Predict Advexin Survival Benefit in Recurrent SCCHN – Preliminary Analysis

T301 Advexin Treated Patients with Informative p53 Profile Data

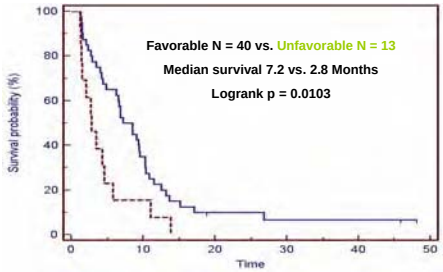


Favorable – High Level WT p53; Low Level Mutated p53; Low Level WT p53
Unfavorable – High Level Mutated p53

MARY CROWLEY CANCER RESEARCH CENTERS

p53 Profiles Favorable and Unfavorable for Advexin Efficacy Predict Advexin Survival Benefit in Recurrent SCCHN – Preliminary Analysis

T201 + T301 Advexin Treated Patients with Informative p53 Profile Data



Favorable – High Level WT p53; Low Level Mutated p53; Low Level WT p53
Unfavorable – High Level Mutated p53

MARY CROWLEY CANCER RESEARCH CENTERS

Summary p53 Molecular Biomarkers Preliminary Results Recurrent Head and Neck Cancer

- **Favorable p53 Biomarker profiles identify patients most likely to benefit from Advexin**
  - **Statistically significant increase survival and disease control**
- **Therapeutic efficacy was obtained with very limited toxicity**

MARY CROWLEY CANCER RESEARCH CENTERS

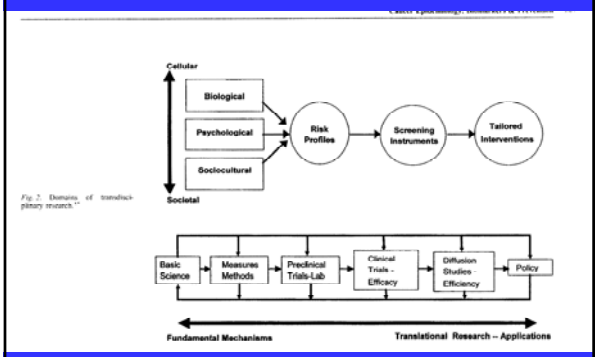
Epidemiology of Prostate Cancer

Summer Program
July 22, 2009
Anthony J. Alberg

Cancer Control:

- "Cancer control research is the conduct of basic and applied research in the behavioral, social and population sciences that, independently or in combination with biomedical approaches, reduces cancer risk."

1997 NCI Report



Best A, et. al. Cancer Epidemiol Biomarker Prev 2003; 12: pg 707.

Ultimate goal is to reduce burden of prostate cancer:

- Prevention
- Early detection
- Prolong Survival

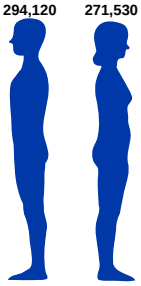
To develop strategies to prevent prostate cancer, we need to understand its distribution in populations

2008 Estimated US Cancer Cases*

		Men 745,180	Women 692,000		
Prostate	**25%**			26%	Breast
Lung & bronchus	15%			14%	Lung & bronchus
Colon & rectum	10%			10%	Colon & rectum
Urinary bladder	7%			6%	Uterine corpus
Non-Hodgkin lymphoma	5%			4%	Non-Hodgkin lymphoma
Melanoma of skin	5%			4%	Thyroid
Kidney & renal pelvis	4%			4%	Melanoma of skin
Oral cavity	3%			3%	Ovary
Leukemia 3%				3%	Kidney & renal pelvis
Pancreas	3%			3%	Leukemia
All Other Sites	20%			23%	All Other Sites

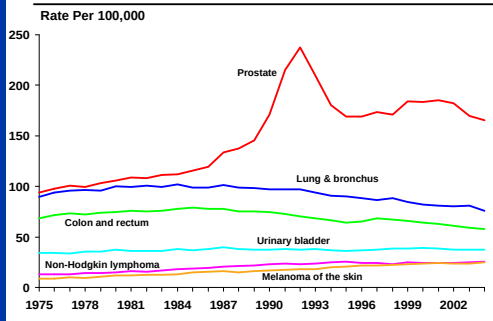
*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
Source: American Cancer Society, 2008.

2008 Estimated US Cancer Deaths*

		Men 294,120	Women 271,530		
Lung & bronchus	31%			26%	Lung & bronchus
Prostate	**10%**			15%	Breast
Colon & rectum	8%			9%	Colon & rectum
Pancreas	6%			6%	Pancreas
Liver & intrahepatic bile duct	4%			6%	Ovary
Leukemia	4%			3%	Non-Hodgkin lymphoma
Esophagus	4%			3%	Leukemia
Urinary bladder	3%			3%	Uterine corpus
Non-Hodgkin lymphoma	3%			2%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%			2%	Brain/ONS
All other sites	24%			25%	All other sites

ONS=Other nervous system.
Source: American Cancer Society, 2008.

Cancer Incidence Rates* Among Men, US, 1975-2004

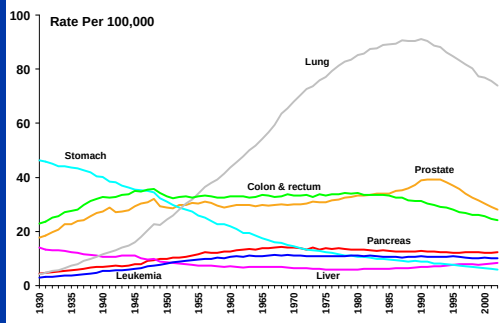


*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting.
Source: Surveillance, Epidemiology, and End Results Program, Delay-adjusted Incidence database: SEER Incidence Delay-adjusted Rates, 9 Registries, 1975-2004, National Cancer Institute, 2007.

Age-adjusted prostate cancer incidence rate by racial/ethnic group, SEER 2002-2006

Group	Rate (per 100,000)
European American	153
African American	240
Hispanic	133
Asian	91
American Indian/Alaskan Native	76

Cancer Death Rates*, for Men, US,1930-2002



*Age-adjusted to the 2000 US standard population.
Source: US Mortality Public Use Data Tapes 1960-2002, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2005.

Cancer Sites in Men for Which African American Death Rates* Exceed White Death Rates*, US, 2000-2004

Site	African American	White	Ratio of African American/White
All sites	321.8	234.7	1.4
Prostate	**62.3**	**25.6**	**2.4**
Larynx	5.0	2.2	2.3
Stomach	11.9	5.2	2.3
Myeloma	8.5	4.4	1.9
Oral cavity and pharynx	6.8	3.8	1.8
Small intestine	0.7	0.4	1.8
Liver and intrahepatic bile duct	10.0	6.5	1.5
Colon and rectum	32.7	22.9	1.4
Esophagus	10.2	7.7	1.3
Lung and bronchus	95.8	72.6	1.3
Pancreas	15.5	12.0	1.3

*Per 100,000, age-adjusted to the 2000 US standard population.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2004, Division of Cancer Control and Population Sciences, National Cancer Institute, 2007.

Cancer Survival*(%) by Race,1996-2003

Site	White	African American	Absolute Difference
All Sites	67	57	10
Breast (female)	90	78	12
Colon 66		55	11
Esophagus	18	11	7
Leukemia	51	40	11
Non-Hodgkin lymphoma	65	56	9
Oral cavity	62	41	21
Prostate	**99**	**95**	**4**
Rectum	66	58	8
Urinary bladder	81	65	16
Uterine cervix	74	66	8
Uterine corpus	86	61	25

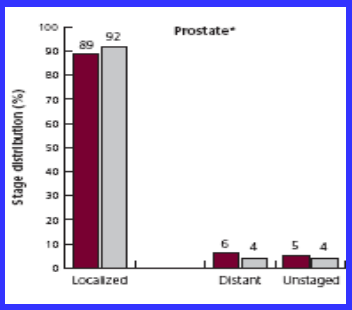
*5-year relative survival rates based on cancer patients diagnosed from 1996 to 2003 and followed through 2004.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2004, Division of Cancer Control and Population Sciences, National Cancer Institute, 2007.

Trends in Five-year Relative Survival (%)* Rates, US, 1975-2003

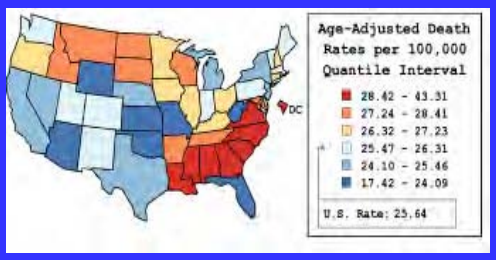
Site	1975-1977	1984-1986	1996-2003
All sites	50	54	66
Breast (female)	75	79	89
Colon 51		59	65
Leukemia	35	42	50
Lung and bronchus	13	13	16
Melanoma	82	87	92
Non-Hodgkin lymphoma	48	53	64
Ovary	37	40	45
Pancreas	2	3 5	
Prostate	**69**	**76**	**99**
Rectum	49	57	66
Urinary bladder	74	78	81

*5-year relative survival rates based on follow up of patients through 2004.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2004, Division of Cancer Control and Population Sciences, National Cancer Institute, 2007.

Stage distribution for AA (red) and EA (gray), US 1996-2004



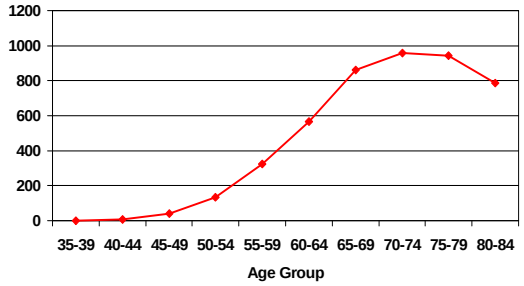
Geographic distribution of prostate cancer mortality rates by state, US 2002-2006

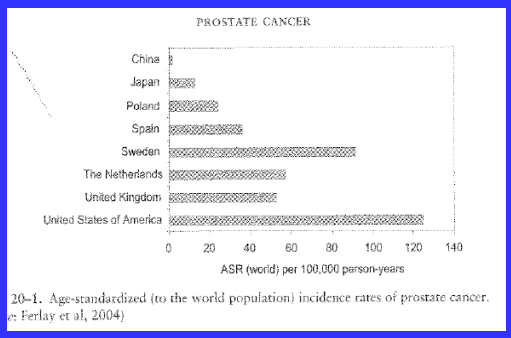


To develop strategies to prevent prostate cancer, we need to understand its causes

The single strongest individual risk factor for prostate cancer is older age.

Age-specific prostate cancer incidence rates (per 100,000), SEER 2002-2006





20–1. Age-standardized (to the world population) incidence rates of prostate cancer. e: Ferlay et al, 2004)

Source: Adami et al.

The results of migrant studies suggest that environmental risk factors are important to the etiology of prostate cancer, but the specific factors have proven difficult to identify.

A significant challenge to epidemiologic studies of prostate cancer is uncertainty about the "disease-free" controls or comparison group

Cigarette Smoking and Prostate Cancer

- Evidence of association with prostate cancer mortality, but not incidence
- Association stronger during 1st 10 years of follow-up
- Hypothesis: Smoking associated with more aggressive disease

Cigarette Smoking and Prostate Cancer

RRs (95% CLs), Washington County, MD
1963-1973 (1st 10 yrs of follow-up)

Smoking Status	Incidence	Mortality
Former	1.5 (0.9, 2.4)	3.2 (1.3, 8.3)
Current >20 cigs/d	1.5 (0.8, 2.9)	3.5 (1.0, 12.4)

Source: Rohrmann S,….Platz EA. J Urology 2007

Summary of Evidence on Dietary Factors and Prostate Cancer

Protects	Risk
Selenium Vit. E Lycopene Vit. D Fish intake	Calcium/Dairy Fat

Source: Adami HO et al

Major inherited susceptibility

- Genetic testing for mutations that confer major inherited susceptibility cannot provide a "cure", but can provide clinically useful information.
- Examples:
  - enhanced surveillance for colorectal polyps (FAP) or breast cancer (BRCA1/BRCA2)
  - organ removal (e.g., prophylactic mastectomy for BRCA1/BRCA2).

  -For prostate cancer, currently none

Common genetic variants associated with small increases in risk

- Ongoing research is attempting to characterize how common genetic variation affects inter-individual susceptibility to prostate cancer (and prostate cancer risk factors)
- A promising lead: 8q24

What steps can we take for the primary prevention of cancer?

Can we take a pill to prevent cancer?

CHEMOPREVENTION

The use of natural (e.g., selenium, vitamin E) or synthetic (e.g., aspirin) to reduce the risk of developing cancer

Examples of chemoprevention: Prostate Cancer

- SELECT Trial
  - –**Bad news:** no evidence that either selenium or vitamin E supplements protects against the development of prostate cancer
  - –~35,000 men followed for ave. 5.5 yrs

Age-adjusted prostate cancer incidence rate by racial/ethnic group, SEER 2002-2006

Group	RR (99% CI)
Placebo	1.0 (referent)
Vitamin E	1.13 (0.95-1.35)
Selenium	1.04 (0.87-1.24)
Both	1.05 (0.88-1.25)

Source: Lippman SM, et al JAMA 2009; 301: 39-

What steps can we take for the secondary prevention of cancer?

Cancer is a fearsome disease, but it is much less fearsome if detected early rather than late.

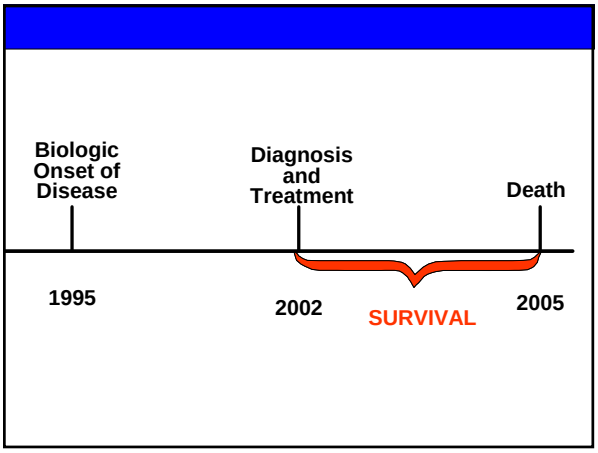
A strong determinant of a cancer patient's survival is stage of disease.

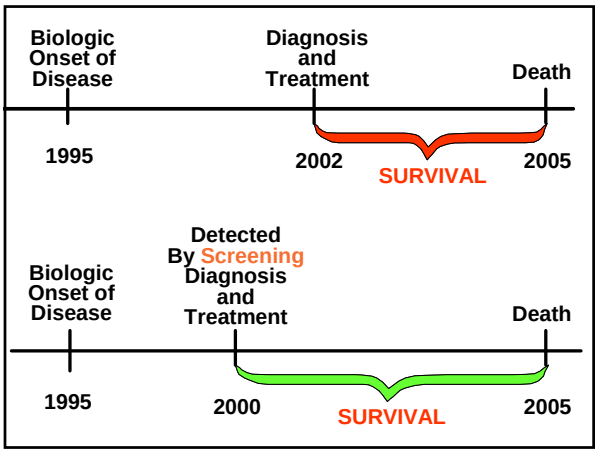
A strong determinant of a cancer patient's survival is stage of disease.

So, a screening test that can shift the population distribution of stage of disease should be embraced, right?

Cancer screening: all that glitters is not gold

- How accurate is the screening test?
- Does the test achieve the intended benefit of reduced mortality? (Is there an effective available treatment that will reduce mortality when cancer is treated earlier?)
- Is the test acceptable to the public?





PSA Testing for Prostate Cancer: Results of RCTs

- 2 randomized controlled trials published earlier this year in New England Journal of Medicine
- Neither study showed significant benefit in reducing prostate cancer mortality
- Strong evidence that PSA testing is not efficacious

PSA Testing for Prostate Cancer: PLCO Trial

- ~77,000 men randomized to PSA testing vs "usual care"
- Intervention: annual PSA testing for 6 years and DRE for 4 years
- 7 years of follow-up
- Mortality rate (intervention vs control): 1.13 (0.75-1.70)

Source: Andriole GL et al NEJM 2009; 360: 1310--

Screening Guidelines for the Early Detection of Prostate Cancer, American Cancer Society

For men at average risk and high risk, information should be provided about what is known and what is uncertain about the benefits and limitations of early detection and treatment of prostate cancer so that they can make an informed decision about testing.

Applied Cancer Screening

- Given a screening test of proven efficacy, research will be needed to identify and overcome barriers to screening

Epidemiology of Prostate Cancer

Summer Program
July 22, 2009
Anthony J. Alberg

MUSC - 6 Colleges

- Graduate Studies
- Medicine
- Pharmacy
- Nursing
- Health Professions
- Dental Medicine

Dr. Cynthia Wright, Assistant Dean for Admissions

wrightcf@musc.edu

The Basics:
What's a Ph.D.?

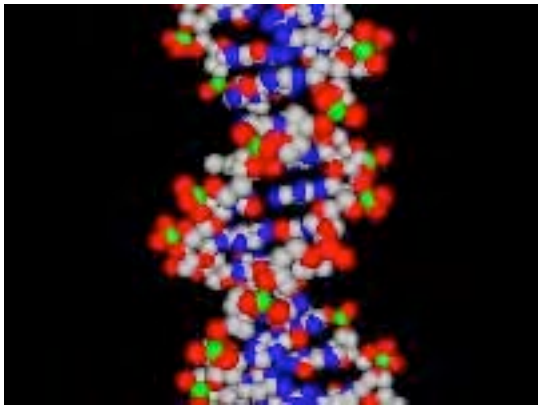
Ph.D.: Doctor of Philosophy degree

- **Highest academic degree earned**
- **Terminal degree**
- **~1% of the population is awarded**
- **Requires:**
  - **Extensive study**
  - **Intense intellectual effort**
  - **Scientific expertise**

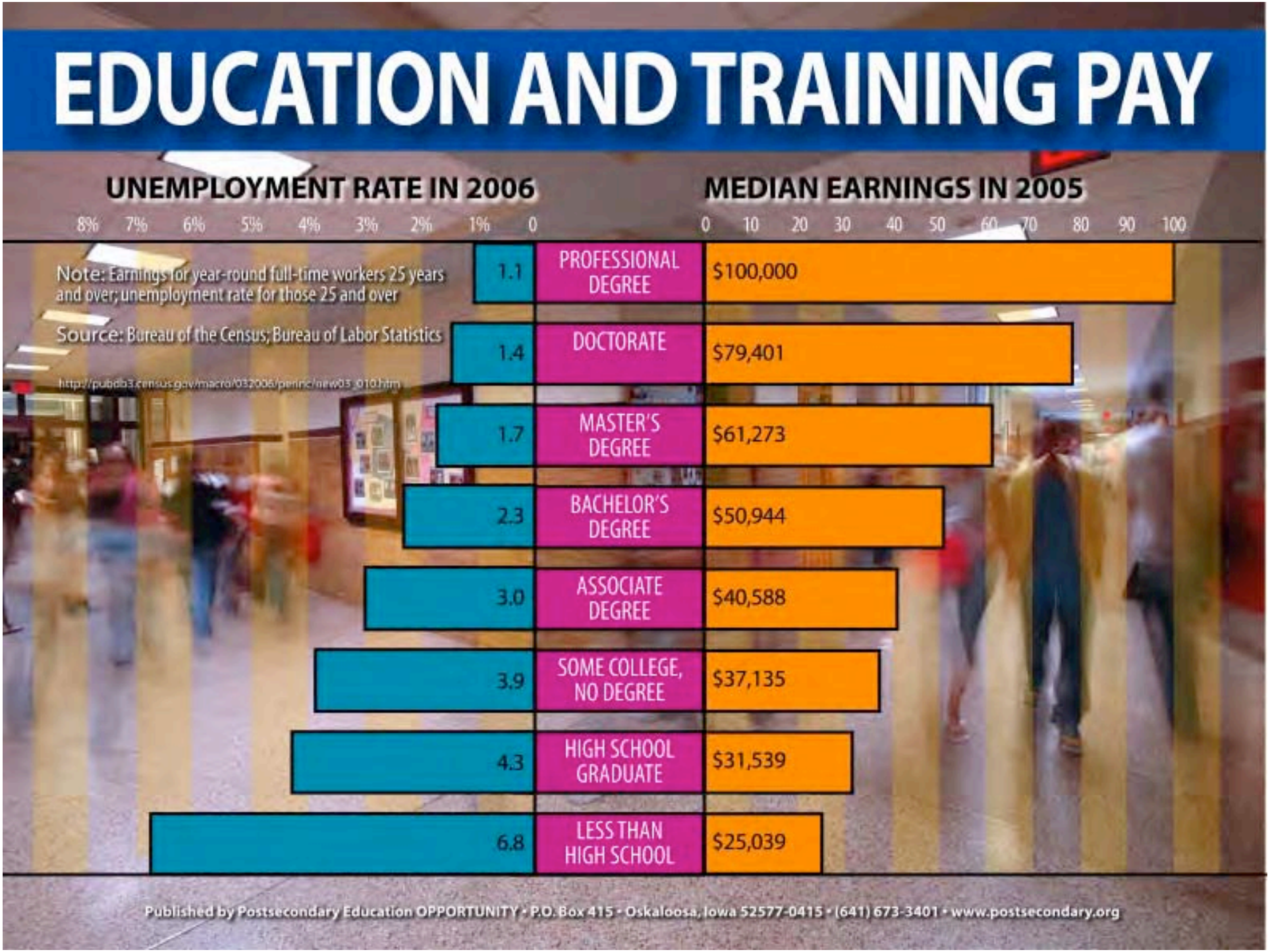
Drs. Brandon, Dansby, Freeman, Hagos, Handy, Owen, and Peprah
Emory University Fellowships in Research and Science Teaching (FIRST)

Benefits of a graduate school degree

- Rewarding career opportunities
  - Make contributions to cutting edge science
- MS and Ph.D required for many positions
- Increased salaries in many biomedical careers
- Flexibility and independence
- Publishing in scientific journals



EDUCATION AND TRAINING PAY



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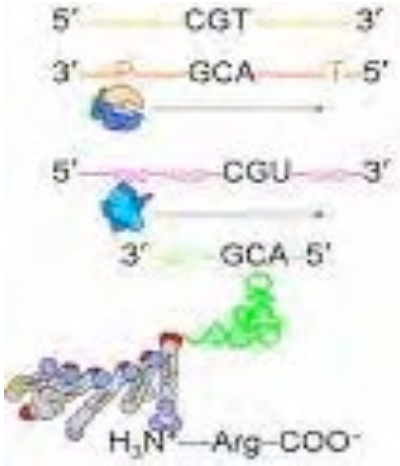
Who Should Do This?

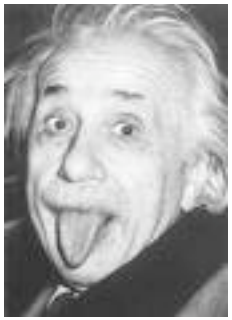
People who:

- **Have curiosity**
- **Enjoy solving problems**
- **Like to work independently**
- **Want to help others**
- **Are flexible about their careers**



McGee and Keller (2007) CBE-Life Sciences Education, 6:316-331.

What can I do with my degree?



Academic Research

Teaching

Industry Research

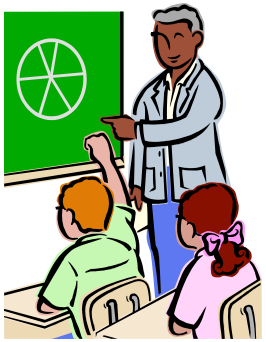
Patent Law

Consulting

Entrepreneur

Medical Writing

Public Policy



Choosing your graduate school

- Make sure that the graduate program fits your interests and goals
- Talk to faculty at your undergraduate institution
- Participate in Summer Undergraduate Research Programs
- Visit the institution
- Discover where graduates have gone

Application Process

- Completed Application (including personal statement and CV)
- Transcripts from all colleges/universities attended
- Letters of recommendation - research mentors
- GRE general test - PREPARE! PREPARE! PREPARE!
- An interview (should) be required - know your research project - goals, aims, outcomes, future directions

Writing an Effective Personal Statement

What are you trying to tell the reader?

1. The reason why you are applying
2. Your short- and long-term career goals
3. Your academic background
4. Past experiences- research and others
5. How (3) and (4) support (2), which then collectively justify (1).

- be coherent, organized, and succinct
- use an active, straight-forward voice
- be specific- get to the point!
- proof, revise, and then proof
- be honest- demonstrate confidence

- don't write a biography or catalog achievements
- don't use clichés, elaborate constructs, etc
- don't quote dead people
- don't lecture!
- don't start out with: I've always wanted to be…
- don't use vague qualifiers: challenging, rewarding, etc

- check your grammar and spelling! NO MISTAKES!!!

What is the proper length?

My infatuation with genetics began the moment I first saw DNA being gently spooled around a glass rod at a summer science program. At that moment this mysterious molecule suddenly became real to me. The potential for manipulating, studying and even altering DNA instantly fascinated me. This experience planted a seed of inspiration in my 13-year-old mind. Since then my innate desire to learn has grown into a love of science and a passion for research. Various experiences helped focus this passion into concrete academic and career goals. One of these goals is to join the Department of Biochemistry and Molecular Biology at the Medical University of South Carolina [MUSC], where I plan to study the genetic basis of disease and explore potential new therapies. My long-term goal is to conduct genetic research in either an industrial or university setting. I plan to use my degree to teach, as well. Many factors have influenced my decision to enter this field, including my undergraduate courses, research experience and some very meaningful extracurricular pursuits.

As an undergraduate I began to discover more about my interests and myself. I found my courses in human genetics and genetic counseling especially appealing. In these courses I enjoyed learning about the unique difficulties associated with diagnosing and managing genetic disorders. In addition I learned the importance of educating the public about genetic disorders during a brief job shadowing experience with a genetic counselor at the UNC [University of North Carolina] Ambulatory Care Center. As a junior, I also got a glimpse of graduate-level courses by taking Principles of Genetic Analysis. This class taught me how to analyze and approach a research topic in the field of genetics. Merely learning about these topics in the classroom, however, was not enough. I wanted the hands-on experience that can only be found in the laboratory.

I took advantage of the research opportunities at UNC and became involved in the Undergraduate Research Program during my sophomore year. I soon found my niche in Dr. Brent Weston?s lab in the Department of Pediatrics. Although I helped with several projects, my main research objective was to develop a viral vector for delivery of an antisense sequence to human colon and liver cancer cells. I used an adeno-associated virus [AAV] vector to package an antisense strand corresponding to part of a human fucosyltransferase gene. This gene produces cell surface molecules that aid in cancer cell adhesion and metastasis. For this project, I collaborated with Dr. Paul Monahan, in the R. Jude Samulski lab at the UNC Gene Therapy Center. Here I learned many of the technical skills I needed in the laboratory. I also interacted with doctoral and post-doctoral students. This further fueled my desire to pursue a graduate degree. The fulfillment I felt when working in the lab convinced me that research was in my future. Despite the many obstacles encountered during my research project, I viewed them as learning experiences rather than barriers to success.

Outside the lab I became involved in Carolina Pediatric Attention, Love and Support [or CPALS], an organization that pairs college students with young people coping with terminal illness. I had the opportunity to meet and connect with two girls, both battling leukemia. This interaction greatly influenced my career goals. It kept my lab work in perspective and focused my research interests on finding better ways to diagnose and treat disease. In addition to CPALS I tutored during my senior year in both Biology and German. Although I had always enjoyed helping classmates informally in these subjects, I felt great satisfaction tutoring other students and watching their progress over time. In addition to their personal successes, I learned from their questions and became a better student in the process. I feel this was good practice for a teaching assistantship. Earning my Ph.D. will open the door to becoming both a researcher and a teacher. Hopefully, my tutoring experience will be the first of many opportunities to teach some of the skills and concepts I have learned.

I have come a long way since that summer many years ago and yet I know that I still have far to go. Once I marveled at the sight of DNA. Now I am interested in such topics as cancer genetics, gene therapy and microarray technology. I have become a strong independent thinker and a creative researcher. Continuing my education is the next step in my development. I hope to draw on my genetic analysis and molecular biology research background as a foundation for studying more advanced concepts. I believe original research is fundamental to acquiring new knowledge and formulating theories. However, applying these theories to real-life situations is just as important, if not more so. I hope to be part of this progression from the lab to the clinic at MUSC. I can find all the tools I need to achieve these goals the Biochemistry and Molecular Biology Department. In addition to its faculty and facilities, the university offers an interdisciplinary curriculum that combines the basic sciences with clinical applications, which is ideal for my interests. Nevertheless, it is my hope that I will be an asset to the university, as well as the department. After completing my doctorate, I hope to study the genetic basis of diseases and develop more efficient treatments for them. My educational and research background is only a part of what I hope to bring to the graduate program - my passion and commitment to this field are equally valuable credentials. I look forward to contributing to the science that has inspired me for so long.

I am in my senior year at Washington & Jefferson College in Washington, Pennsylvania. I am a Cell/Molecular Biology Major. After my undergraduate studies at W&J I would like to further my education in graduate school in pursuit of a doctorate in Biomedical Sciences. At Washington & Jefferson I have a GPA of 3.02 overall and a 2.82 in my major. Over the past two years at W&J my major GPA is 3.0.
I have completed numerous miniature research projects in many different biological capacities. Washington & Jefferson is a small research-intensive college, which has provided me various opportunities to do independent research. I have done two, four-week research projects. The first examined the effect of Ibuprofen on malignant cells. The second research project examined glutamate receptors in the retina of juvenile tiger salamanders. Also, through a summer class taken in conjunction with Cornell University, I did a four-week transect study examining population disbursement and predator/prey relations of the intertidal region of Appledore Island, Maine.
My current research interests include both facets of my previous research. I am very interested in looking at marine aspects and the molecular biology concepts that I am currently studying. I feel that the Medical University of South Carolina is a perfect fit with their program in Marine Biomedicine.
I am currently interested in pursuing a graduate degree in order to become more specialized in a major that infatuates me. An undergraduate degree is not sufficient in order to pursue my lifelong goals. My long-term goals are to obtain my doctorate in Marine Biomedicine and pursue a research career. After developing some experience in the field, I would like to teach in an academic institution.

One page is good- 1/3rd to 1/4th of a page is not

Tips on Preparing a Curriculum Vitae (CV)

“Course of Life” is the Latin translation of Curriculum Vitae.

What goes into a CV ?

Contact information

Who are you? Where are you from? Here, include your name, address, phone, fax, and e-mail for home and office, if applicable.

Education

Indicate your major, type of degree, and the date each degree was awarded for each postsecondary school attended

Teaching Experience List any courses that you assisted with as a TA, co-taught, or taught.

Conference Presentations

Similar to the section on publications, separate this category into sections for posters and papers. Use the appropriate documentation style for your discipline.

Professional Activities

List service activities, committee memberships, administrative work, lectures you've been invited to deliver, professional workshops you've delivered or attended, editorial activities, and any other professional activities in which you've engaged.

Professional Affiliations

List any professional societies with which you're affiliated, Honor or Scientific Societies, Student affiliate

Research Interests

Briefly summarize your research interests with four to six key descriptors. This is best added during graduate school than before.

Research Experience (Very important)

List assistantships, summer undergraduate programs, and other research
experience. Include the institution, nature of the position, duties, dates,
and supervisor.

Grants Awarded

Include title of agency, projects for which funds were awarded, and dollar amounts.

Publications

Put the full reference

References

Get permission ahead of time. Make sure they will speak highly of you.

What Not to Put In

Don't overly personalize.

Pretty Cool People Club

Doughnut Appreciation Club

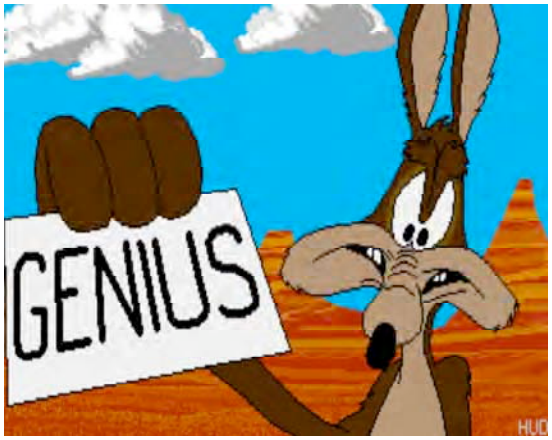
Fernando

Padding

Don’t list lots of projects underway
Don’t have more form than substance

No Padding!

Don’t Exaggerate



OR

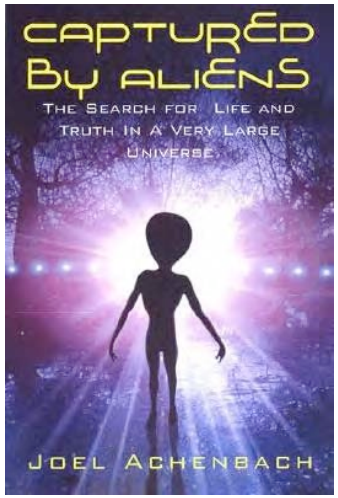
Other considerations when preparing a CV:

QUALITIES OF AN EFFECTIVE CV

* Easy to read
* Clear and concise
* Comprehensive but concise
* Correct
* Be Honest

CURRICULUM VITAE DISASTER AREAS

* Poor appearance or format
* Confusing or illogical organization
* Incorrect grammar or word usage, misspellings, typographical errors
* Poor photocopy
* Lack of name, address or phone number
* Unexplained time periods



* Exaggerations or "padding”

* Insufficient or contradictory information

MUSC
COLLEGE of GRADUATE STUDIES

Degrees Offered

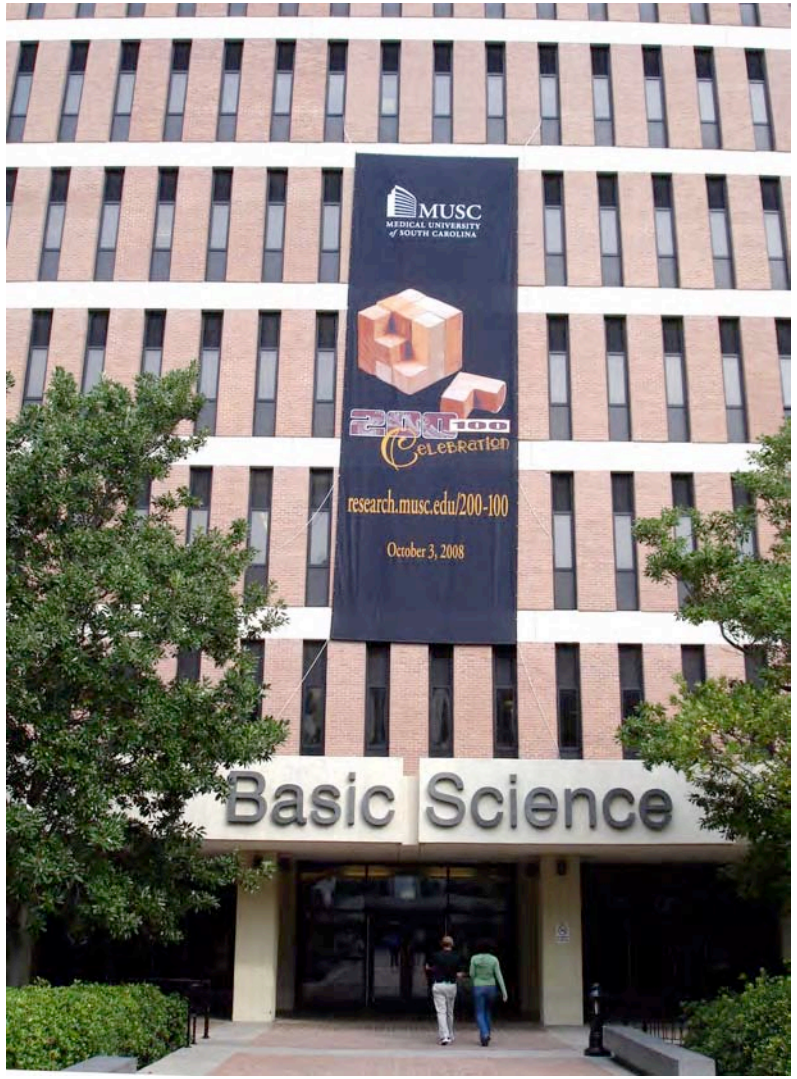
MS

PhD

MD/PhD

PharmD/PhD

DMD/PhD



MD/PhD Application Process

- **Apply through AMCAS**
- **Apply online to MUSC MSTP program**
- **MCAT scores (32)**
- **GPA (3.5)**
- **Letters of recommendation**
- **Interview**

Research experience is critical

MD/PhD Pathway:

- First 2 years of medical school (lab rotations in the summers)
- Step 1 USMLE
- 3-4 years research
- Final 2 years of medical school

Graduate!

PhD Application Process

- **Completed Online Application (including personal statement and CV)**
- **Transcripts from all colleges/universities attended (3.0 GPA or greater) (3.4)**
- **Letters of recommendation (3)**
- **GRE general test (guideline is 1100 V+Q) (1220)**
- **Interview**
- **TOEFL test if international**

Research experience is critical

PhD Pathway:

- First year core (interdisciplinary) curriculum
- Choose a program and a mentor/laboratory
- Advanced course work (12 hours)
- Written and oral qualifying exams
- Dissertation research
- Defend your dissertation

Graduate!

~5 years

Financial considerations

Stipend $23,000-25,000/year

Paid health insurance

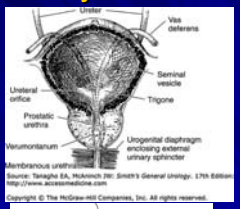
Dean’s scholarship for tuition

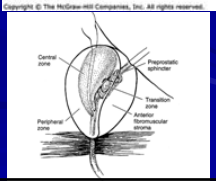
The role of Prostate Specific Antigen (PSA) in Prostate Cancer Research

Stephen J. Savage, MD
Associate Professor
Director of Minimally Invasive Urology
Medical University of South Carolina
Charleston, SC USA

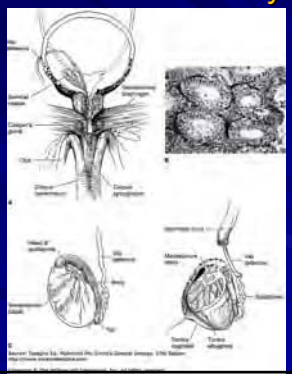
Prostate Anatomy

- Helps to condition ejaculate
- Located between bladder and external urethra
- Where genital and urinary tracts meet





Prostate Anatomy



Prostate Cancer

- Cancer (malignancy) is a description of unregulated growth of cells in the body
- The body's cells continue to turnover (die and replenish) over a lifetime
- Many cellular regulatory processes help to determine how quickly these happen
- Escape from this regulation is most often the inciting event in the development of a cancer
- Many other factors need to occur to allow this unregulated growth to continue and then to adversely affect the body

Prostate Cancer

- Approximately 230,000 men are diagnosed yearly
- Second leading cause of cancer death in men
- Incidence continues to increase with age
- Autopsy studies show many men die **with** prostate cancer
- Lifetime risk of latent cancer in 50-year old is 40%, clinically apparent 9.5%, death 2.9%
- Even in important prostate cancer, it is a relatively indolent disease
- How do we detect/monitor this?

PSA

- Identified in 1985
- Enzyme made by the **normal** prostate epithelium
- Secreted into seminal fluid to liquify the seminal coagulum
- Blood tests measure the amount detectable in the bloodstream
- After discovery, banked blood showed that patient's ultimately diagnosed with prostate cancer had elevated PSA

Prostate Cancer Detection

- Screening by yearly digital rectal examination and serum PSA measurement
  - 50 years old (40 for African-Americans and family history)
- Controversial based on over-treatment after diagnosis
- PSA elevation determined at 4 ng/ml
  - Positive predictive value at 20-30% at PSA 4-10
- Subsequent studies question the validity of this cutpoint.
- Ultrasound-guided prostate needle biopsy is required to make diagnosis of cancer

PSA Testing in Prostate Cancer

- If PSA is made by normal prostate, how can we effectively use it for diagnosing prostate cancer?
- Once the prostate is removed surgically, the PSA becomes completely undetectable
- Surgery is not the only method of treating prostate cancer
  - Radiation
  - Chemotherapy
  - Hormone blockade
- How can we improve PSA as a tool to monitor prostate cancer as well as the effectiveness of treatments?

PSA as a Tumor Marker

- Cancers can be measured by looking at visible tumor on scans.
- Prostate cancer commonly produces PSA regardless of where it is growing
- The presence of detectable PSA may indicate the continued presence of cancer despite no change in imaging studies

PSA as a Tumor Marker

- Since PSA is made by normal prostate it does not (always) equate to the presence of prostate cancer
- It may be the only indication of the potential presence of disease
- Since it is associated with the possible presence of disease it is a **surrogate** marker
  - A representation of disease that should be associated with presence/absence, growth/death of disease

Surrogate markers

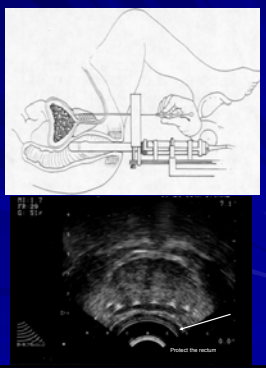
- The perfect surrogate marker will have direct correlation with its behavior and the behavior of the cancer
  - Absence of cancer = absence of marker
  - Doubling of cancer = doubling of marker
  - Response to therapy = decrease of marker
- Multiple medical research studies have made grave mistakes in overestimating the importance of a surrogate marker as well as the ultimate response
  - Does lowering cholesterol decrease heart attacks?
  - Does better glucose control improve health of diabetics?
  - Does improving rhythm control reduce death in cardiac patients?
  - Does improving PSA mean that cancer is responding?

PSA as a Surrogate marker

- Initial tests were able to detect PSA <0.1 ng/ml
- Refinement in techniques allowed super-sensitive assays <0.001
- Subsequently determined that some periuretheral glands can secrete small amounts of PSA
  - Not an exact surrogate marker
  - What do we do with patient's who have PSA of 0.03?
  - What do you tell a patient who has his PSA change from 0.001 to 0.02?
  - **PSA ANXIETY!**

PSA as a Surrogate marker

- PSA becomes undetectable after successful surgical removal
- Radiation therapy does not always result in undetectable PSA
- Radiation can be delivered externally as well as with seed implantation of the prostate
  - Seed implantation results in PSA "bounce at 18-24 months
- Various definitions of success exist
  - 3 rising PSA values
  - PSA >0.2, >0.5, etc



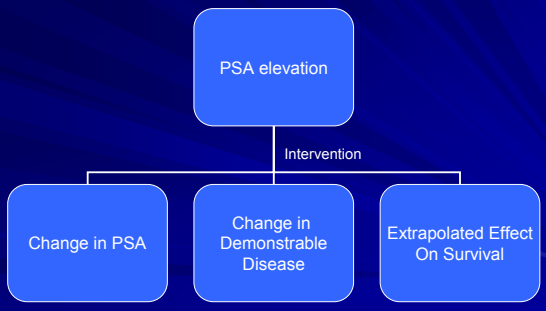
PSA as a Surrogate marker

- Historically, prostate cancer that has spread outside of the prostate is termed metastatic disease
- Since 1940, the mainstay of treatment for metastatic prostate cancer has been androgen (hormone) ablation
- This only controls the disease, but does not cure it
- Survival is improved while the disease is treated
- Androgen ablation shown to have a dramatic effect on PSA.
- Rising PSA predates demonstrable disease by 12 months – 3 years in hormone refractory disease
- Since there is known effect and relationship, PSA was used as a surrogate marker

PSA as a Surrogate marker

- With the advent of PSA, a new stage of prostate cancer developed
  - Detectable PSA, without any other visible disease (presumably micrometastatic)
- Rather than treating when radiographic disease developed, patients were treated when the PSA rose
- Outside of androgen ablation, there were no known effective agents
- It is clear in other cancers, that the lower the burden of disease, the more beneficial the potential effect of systemic therapy (chemotherapy)
- Given the time course of progression of prostate cancer, PSA values are attractive as potential more detectable and measurable changes

PSA as a Surrogate marker



PSA as a Surrogate marker
Pitfalls

- Often times there were unclear modes of action with various systemic therapies
  - Estramustine (chemotherapy) had clear estrogenic effect
  - PC-SPES (herbal remedy) showed PSA benefit, but was subsequently found to have estrogenic effect
- Various factors can regulate PSA production
  - Dietary effects
  - Differentiated vs. undifferentiated disease
- Although PSA production clearly has some relationship to burden of disease, it is sometimes beneficial
  - Intermittent androgen deprivation

PSA as a Tumor Marker
Improvements

- Diagnosis
  - Age-specific PSA
  - PSA density
  - Free and complexed PSA
  - PSA velocity
  - PSA doubling time
- Prognosis
  - PSA velocity
  - PSA doubling time
  - Molecular markers
- Combination with other factors
  - Gleason score
  - Radiographic disease
  - Molecular markers

Study Design

- You have a new treatment that can kill prostate cancer cells in the laboratory
- It has been shown to decrease the number of measurable cells
- Preliminary studies have shown that it is not toxic to humans
- How are you going to design your cancer research trial?

Study Design
Concerns

- Most importantly - demonstrate a significant survival difference between treatment and no treatment (placebo-controlled)
  - Statistician determines how large a difference is needed and how many patients are required
- Prostate cancer is a relatively slow-growing disease and the time from known recurrent or metastatic disease to death is measured in years
  - Consequently, survival advantage will take many years to determine
  - Patients are aware of changes in measurable disease and may not be willing to wait to answer question of survival
  - The overall costs become exponentially higher to continue a long study vs. shorter study
- What about PSA?

Study Design
Concerns

- Virtually all patients enrolled in this trial will have elevated PSA.
  - Differentiated cancer makes more PSA
- If the PSA responds, this typically occurs quickly and can be measured in % response
  - How does one remove confounding variables?
- The study time will be dramatically contracted (failure or success)
- Patients would potentially be eligible for other studies.
- ***Is this equivalent to a survival advantage?***

PSA Summary

- Extremely useful tumor marker
- Multiple confounding factors that make it more difficult to use (not +/-)
- Public (and non urologic physicians) knows it exists, but poorly understands the variability
- Potential large advantage as surrogate marker if it continues to correlate (loosely) with survival

APPENDIX C.

Student Fellow Scientific Research Papers

Scharan Clarke

Claflin University

Authors: Sharan Clarke, Matthew McIntyre, Harry Clarke, Stephen Savage

Does The Preoperative Evaluation Of Men With Bladder Outlet Obstruction Affect The Outcomes Of Outlet Reduction Procedures?

Objective: Evaluate whether preoperative workup affects surgical outcomes in patients with symptomatic urinary obstruction. Noninvasive uroflow and check of post void residual urine has traditionally been adequate assessment for non complicated patients with symptomatic obstruction. Recent literature has not shown invasive urodynamic testing to be of clinical benefit to patients receiving bladder outlet reducing procedures. However, it has been shown to better delineate patients who will receive maximal benefit and avoid complications from outlet reduction. We evaluated our series to see if we had clinically significant out come differences.

Methods: We retrospectively reviewed our series of 119 patients extracted randomly from 2004 to 2009. These patients were selected by procedure code for both electrosurgical resection and photovaporization of the prostate. Patients were evaluated on preoperative factors including: IPSS, cystometrogram (CMG) or noninvasive uroflow, incontinence, retention, prostate size, and use of medical therapy. Intraoperative characteristics evaluated included: surgical procedure, operative time, hospital stay, catheterization time, complications, and the presence of an intravesical lobe. Postoperatively we evaluated: IPSS, noninvasive uroflow, recatheterization, reinitiating of medical treatments, de novo incontinence, and follow up.

Results: We found 119 patients who had undergone outlet reducing procedures. Nine patients were excluded from the study because obstruction was secondary to malignant processes. 68 (57%) underwent electrosurgical resection and 51 (43%) underwent photovaporization of the prostate. The mean preoperative IPSS was 18 with QOL score 3. We organized patients in to three groups based on preoperative testing. Thirty two (29%) patients underwent CMG, 35 (32%) underwent noninvasive uroflow, 43(39%) had no preoperative urodynamic testing. The mean PVR was 199mL and 153mL respectively. The mean prostate size was 48cc, 44cc and 52cc respectively. Two patients in each group had incontinence preoperatively 6% for CMG and noninvasive 5% of untested. Retention was present in 9 (28%), 2 (6%), 3 (7%) respectively. Preoperative use of medical therapy was seen in 24(75%), 32(91%), 29(67%) respectively.

Operative time was lowest for patients with noninvasive studies with a mean of 55 minutes then CMG at 59 minutes and no studies at 67 minutes. Hospital stay was shortest with noninvasive testing mean of 0.4 days. CMG had a mean of 0.96 days and those with no testing stayed 1.2days. Catheters came out first in those with noninvasive testing mean of 1.2 days, 1.3 with no testing, and 1.9 days with CMG. Two complications were noted in both the noninvasive group and those without testing.

Post operatively the mean IPSS was 11.2 in the CMG group, 10 in the noninvasive, and 9.4 in those without studies. This is a change of 9.2, 9.5, 5.6 points respectively. Mean peak flow and PVR were 13ml/sec, and 119cc; 11.7ml/sec, and 118cc; 9ml/sec and 90cc respectively. One patient (2%) had de novo incontinence in the noninvasive group. Five (15%) patients in the CMG group, 4(11%) in the noninvasive, and 1(2%) in the non studied group required recatheterization. Medical therapy was reinstituted in 7 (21%), 4(11%), 1(2%) patients respectively. Mean follow up was 15.7 months in the CMG group, 20 months in noninvasive, and 16 months in those without studies.

Conclusions: In our series more invasive preoperative evaluation did not lead to better clinical outcomes based on recathterization rates, IPSS, or restarting medical therapy. However, intraoperative complications were more common as was de novo incontinence with less invasive testing.

Andrea Gibson
Claflin University

Enhancing Gene Delivery To Cancer Cells

Introduction

Prostate cancer is a cancer that forms in tissues of the prostate. The prostate is a gland in the male reproductive system found below the bladder and in front of the rectum. The American Cancer Society has estimated that in the year 2009 alone that there will be 192,280 new cases of prostate cancer and 27,360 deaths. This cancer is the most commonly found in men in the United States. It is even more of a threat to African American men. African American males are found to be at twice the risk of prostate cancer compared to Caucasian men. Why is this so? Researchers suspect that prostate cancer in African American men is due to an inherited gene. Studies are under way for more detail on this gene.

An adenovirus is a DNA containing virus which can cause respiratory disease, which may include the common cold. Adenoviruses can also be genetically modified and used in gene therapy to treat diseases such as cystic fibrosis and in the case of this project, cancer. Adenoviruses are commonly used due to the fact that they can infect many different cell types with high effectiveness. Adenovirus enters a cell by a surface protein known as coxsackie and adenovirus receptor (CAR) which functions as an adhesion protein (Kasman et al. 2009). However CAR expression is often decreased in cancer cells and this becomes a problem for delivery of adenovirus. Researchers are looking into numerous solutions. Two solutions are closely examined in this project.

HDACi are materializing into an exciting new class of potential anticancer agents for the treatment of solid and hematological malignancies. In recent years, an increasing number of structurally diverse HDACi have been modified that inhibit proliferation and induce differentiation and/or apoptosis of tumor cells in culture and in animal models. HDAC inhibition causes acetylated nuclear histones to accumulate in both tumor and normal tissues, providing a surrogate marker for the biological activity of HDACi in vivo (Visgushin and Coombes, 2002). HDACi increase adenoviral transgene expression which lowers the amount of adenovirus needed to achieve a therapeutic response, therefore offering a probable solution to increasing adenoviral delivery (Kasman et al 2007).

Polymers are an arrangement of replicated structural units normally connected by covalent bonds. They have high melting and boiling points. Polymers have been utilized to improve “adenovirus-mediated gene delivery”. Previous studies have shown that cationic polymers poly-L-lysine and poly (ethylene imine) have enhanced adenoviral infection but because of their toxicity, have a limited use (Kasman et al. 2009).

Methods and Materials

Materials

Prostate cancer cells of the cell line PC3 and 22RV1 which were grown in RPM1 plus 10% fetal calf serum and an antibiuotic/antimycotic solution. HDACis depsipeptide and MS275 were obtained from the CTEP program at NIH and Calbiochem (San Diego, CA) respectively. The polymer called EDGE-3,3’ was kindly provided by Dr. Kaushal Rege, Arizona State University. AdGFP is a virus described previously in which the GFP transgene is expressed from the CMV promoter (Kasman et al. 2009).

Method

For adenoviral transduction, cells were plated overnight at $2x10^5$ cells/well in a 12-well plate. The following day, AdGFP was diluted in medium to the appropriate multiplicity of infection. Cells were then treated with AdGFP in the absence or presence of HDACi. For the experiments with polymers (stock 10mg/ul), virus was diluted to the appropriate MOI and pre-incubated with polymer for 10 minutes at room temperature. After the 10-minute incubation, 100 ml/well of media was added to the tube and the medium in each well was replaced with polymer/virus mixture. Cells were assayed for GFP expression and cell death 48-hours post-infection.

All cells were included in the analysis for flow cytometry. PBS was added to the tube consisting of the spent media. After the cells were detached from the wells by the trypsin, they were pooled with the any non-adherent cells. Cells were pelleted at 1000 rpm for 10 minutes and pellets resuspended by PBS. 350 ul of 10% formalin was placed in each sample to fix the cells. Samples were analyzed by the MUSC flow cytometry core facility using a FACSCalibur.

Results and Discussion

PC3 treated with AdGFP + Drug

The cell line PC3 infected poorly than the 22RV1 cells. Therefore, because of the goals that were trying to be accomplished, it was most fitting to carry out the remainder of the experiment using PC3 cells. After cells had been plated, the next day they were treated. The treatment included 6 wells that contained AdGFP with no drug, 6 wells with AdGFP and depsipeptide, and 6 wells with AdGFP and MS275. The results showed that the PC3 cells with AdGFP and depsipeptide had an increased infectivity. This was followed by cells with AdGFP and MS275, and the cells with no virus had less infectivity.

PC3 treated with AdGFP + Polymer

After 24 hours since plating, the cells were treated with virus and polymer. Each well received the same amount of virus which was 2 ul. 6 wells received no polymer at all, 6 wells received 2 ul of polymer, and 6 wells received 4 ul of polymerase. The difference in this trial was the MOI which was as follows: 0, 1, 3, 10, 30, and 100. The results showed that the polymer did not increase infectivity. Each the wells with 2ul and 4ul of polymer had relatively the same amount of infectivity as the wells that received no polymer at all.

This study is similar to a previous one that looked at “polymer-enhanced adenoviral transduction of CAR-negative bladder cancer cells.” The results from the study showed that the polymer EGDE-3’3 can enhance transduction of adenovirus and transgene expression in cells that do not have CAR expression. However, this experiment showed otherwise. The EGDE -3’3 polymer did not enhance transduction and therefore it did not increase the infectivity of the PC3 cells. One reason that my explain this is that perhaps some of the PC3 cells were experiencing apoptosis and therefore did not respond well to infection.

Conclusion

In conclusion, EGDE-3’3 with AdGFP did not enhance infectivity in PC3 cells. However, there was an increase when HDACi were used along with AdGFP. There was a notable increase of infectivity in the cells that were treated with AdGFP and depsispeptide. Cells treated with MS275 and AdGFP did have an increase in infectivity but not as much as those with depsipeptide. In the future, studies should include another cell line and treat as such in this experiment. There should be an investigation as to why the polymer did not work as well in this experiment as it did with the bladder cells.

Figure 1

PC3

MOI	% of GFP +	GFP Intensity
0	0.06	552.32
10	11.93	44.05
30	19.66	83.39
100	24.93	161.13
300	32.54	228.33
1000	46.22	255.88
3000	62.91	297.36

22RV1

MOI	% of GFP +	GFP Intensity
0	0.76	116.52
10	82.93	797.67
30	54.56	462.32
100	82.85	1558.35
300	86.83	2472.25
1000	61.06	584.11
3000	92.55	2492.63

A

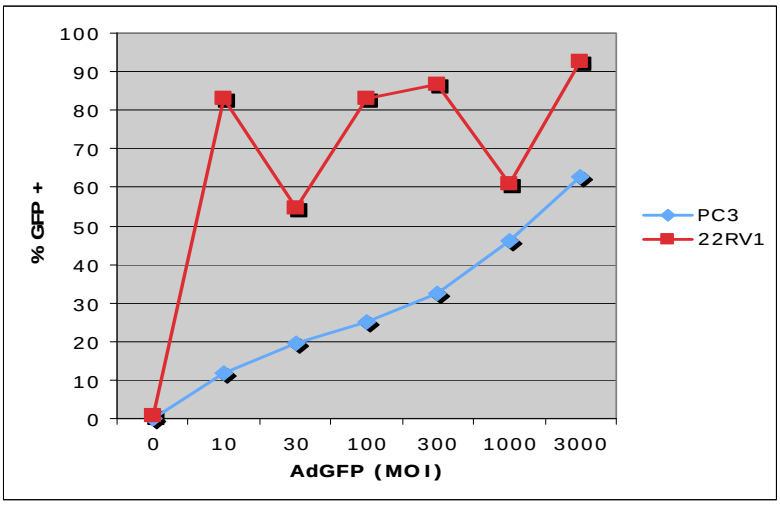


Figure 1A. Adenoviral infectivity. Prostate cancer cells from the cell lines PC3 and 22RV1 were plated overnight and infected with AdGFP.

B

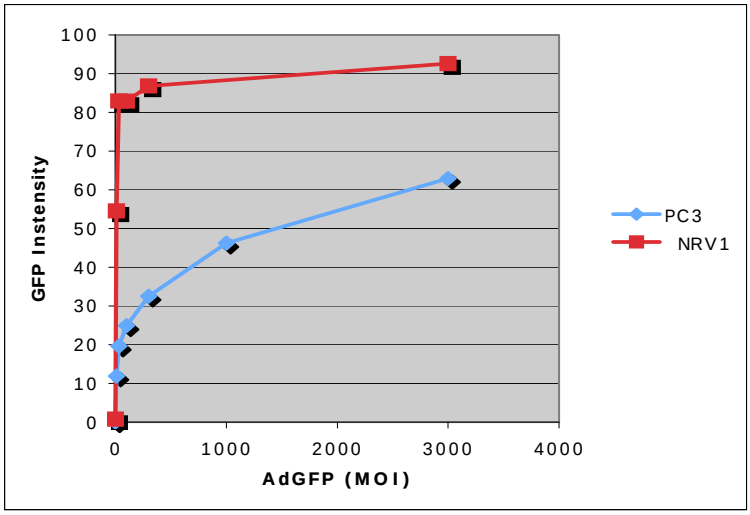


Figure 1B. Adenoviral infectivity. Prostate cancer cells from the cell line PC3 and 22RV1 were plated overnight and infected with AdGFP.

Figure 2

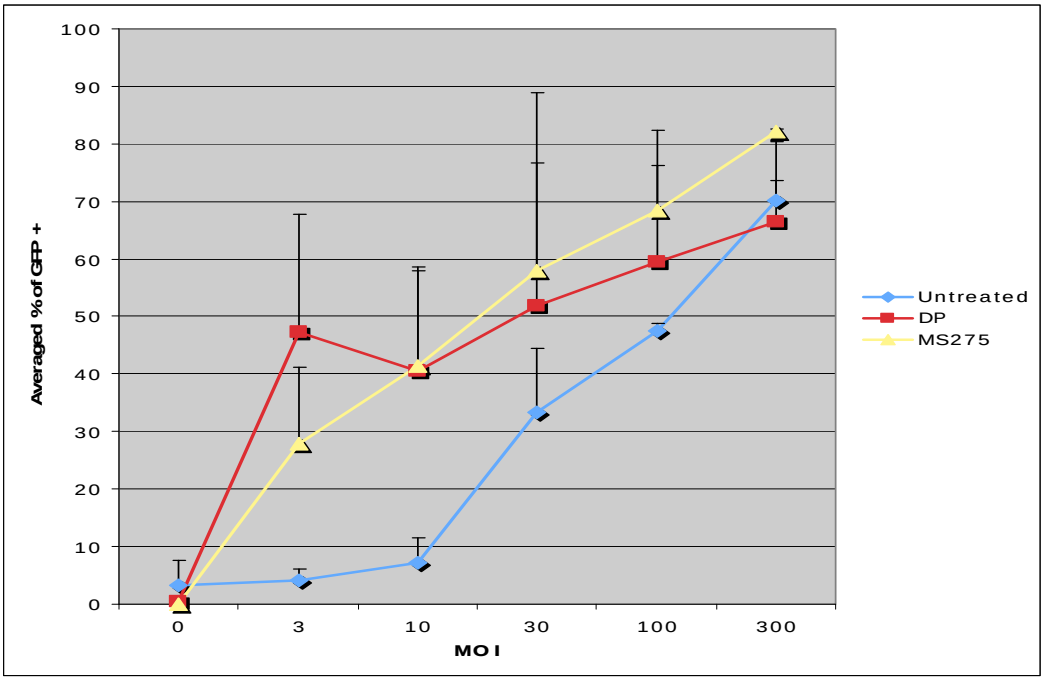


Figure 2. PC3 cells were plated overnight and treated with a virus-drug mixture. Results revealed that cells infected better with AdGFP and depsipeptide.

Figure 3

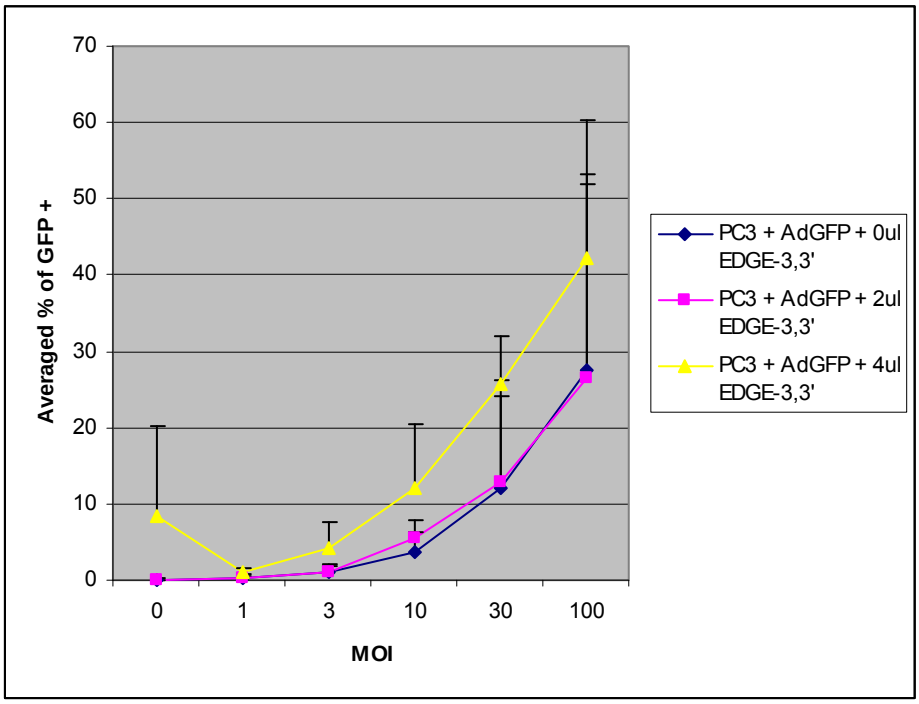


Figure 3. PC3 cells were plated overnight and were treated with a virus- polymer mixture. As a result, it was noticed that polymers *did not* enhance the infectivity of cells with AdGFP.

PC3 + AdGFP + DP

MOI	PC3 1	PC3 3	Average	Standard Deviation
0	0.31	0.69	0.5	0.26
3	32.7	61.68	47.19	20.49
10	27.63	53.31	40.47	18.15
30	69.42	34.46	51.94	24.72
100	71.29	47.53	59.41	16.80
300	56.63	76.27	66.45	13.88

PC3 + AdGFP + MS275

MOI	PC3 1	PC3 3	Average	Standard Deviation
0	0.02	0.06	0.04	0.02
3	18.55	37.23	27.89	13.20
10	29.74	53.15	41.445	16.55
30	36.1	79.9	58	30.97
100	58.49	78.31	68.4	14.01
300	82.4	81.78	82.09	0.438

Average % of GFP +

MOI	UT	DP	MS275	untreated std	DP std	MS275 std
0	3.17	0.5	0.04	4.49	0.26	0.02
3	4.2	47.19	27.89	1.96	20.49	13.20
10	7.26	40.47	41.44	4.34	18.15	16.55
30	33.38	51.94	58	10.96	24.72	30.97
100	47.51	59.41	68.4	1.20	16.80	14.01
300	70.155	66.45	82.09	3.54	13.88	0.43

PC3 + AdGFP + 0ul EDGE-3, 3'

MOI	Trial 1	Trial 2	Average	Standard Deviation
0	0.01	0.2	0.105	0.134350288
1	0.56	0.14	0.35	0.296984848
3	1.87	0.26	1.065	1.138441918
10	6.62	0.57	3.595	4.277996026
30	21.97	2.08	12.025	14.06435388
100	50.74	4.19	27.465	32.91582066

PC3 + AdGFP + 2ul EDGE-3, 3'

MOI	Trial 1	Trial 2	Average	Standard Deviation
0	0.01	0	0.005	0.007071068
1	0.67	0.05	0.36	0.438406204
3	1.69	0.55	1.12	0.806101731
10	4.98	6.07	5.525	0.770746391
30	20.82	5.08	12.95	11.12986074
100	45.33	7.51	26.42	26.74277846

PC3 + AdGFP + 4ul EDGE-3, 3'

MOI	Trial 1	Trial 2	Average	Standard Deviation
0	0	16.68	8.34	11.79454111
1	0.55	1.39	0.97	0.593969696
3	1.79	6.64	4.215	3.429467889
10	5.87	17.99	11.93	8.570134188
30	21.18	30.2	25.69	6.378103166
100	49.09	35.49	42.29	9.616652224

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CoDanielle Greene
SC State University

Role of ABCA2 in Prostate Tumor Progression

Introduction

The ATP-binding cassette transporter 2 (ABCA2) is an endolysosomal protein most highly expressed in the central and peripheral nervous system tissues and macrophages. Profuse ABCA2 expression in cancer cells has been proven to be associated with resistance to chemotherapy and multi-drugs. Previous studies have indicated its role in cholesterol/steroid (estramustine, estradiol, and progesterone) trafficking/sequestration and shown its expression during macrophage and oligodendrocyte differentiation, processes that entail membrane growth. This is the reason that this study focuses on determining the role of this specific protein, in order to inhibit the incidences of multi-drug resistance and tumor relapse.

The hypothesis of the study is that the role of ABCA2 expression has an effect on the growth response of the TRAMP model of prostate tumor development and progression. To investigate the hypothesis, the study requires determining if ABCA2 is indeed correlated with tumor progression and whether ABCA2 has an effect on the grade of prostate tumors and instances of metastasis.

Materials and Methods

Western Blotting Analysis

Materials- semi-dry transfer apparatus or wet transfer apparatus, filter paper (regular and extra thick), PVDF membranes, hydrating solution for the membranes (in this case, solution used was Methanol), running buffer(10x), transfer buffer(10x), forceps, test tubes, graduated cylinders, gloves, lab coat, gel electrophoresis apparatus, proteins antibodies, and antigens

Method

- Make the gel- depending on what type of gel needs to be made, for a 10% gel, combine 9.75ml dH2O, 5ml of 1.5M Tris-HCL phs 8.8, 4ml acrylamide, 200ul SDS, 100ulAPS, and 20ul TEMED. Add a layer of Butanol over the edge and wait 15 min for the gel to solidify. Then add satacking gel, combing 6.79ml dH20, 2.5ml of .5M Tris-HCL phs 6.8, 1ml acrylamide, 100ul SDS 59ulAPS, and 10ul TEMED.
- Place the gel into the electrophoresis apparatus and load the protein into wells. Transfer the gel onto a membrane.
- Detect target protein with a specific primary antibody and probe with specific secondary and tertiary antibodies, then image the blots

Polymerase Chain Reaction

Materials- ice to keep primer and master mix cool, mini pipette case to hold tubes, micropipettes, FWD and Reverse primers, 2x Master Mixx, ddH20, and template DNA.

Method

- Make the Master Maxx. And add the DNA. Amplify DNA in the thermocycler
- Load samples into the gel and run PCR on apparatus

IHC for Vimentin and Desmin

Materials

Vimentin	Desmin
6 samples	" "
1200 ul 1.2 Triton X-100	" "
120ul goat serum(10%)	" "

600ul 1% BSA/PBS " "
4ul secondary Vimentin 3ul secondary Desmin
Method

- De-wax slides
- Rehydrate with dH20
- Antigen Retrievel 20-30 min 10mm citrate buffer
- Ph6.0 wash 2x PBS
- Block in 3% H2O2/ MiOH 20 ml in 180 ml
- Sit slides out for 1hr room temp
- Secondary Ab 45ul rabbit IGf-biolin in 1500 ul PBS
- Add 197 ul to each slide and incubate @ room temp for 30 min
- Add ABC readent and incubate

Scratch Assay
Materials- D6P2T cells, Schwanoma (rat cell line), pipette tip, and 3 cm plates
Method

- Take a pipette tip and scratch a straight line into a cell monolayer
- Capture images during cell migration to close the scratch at 0h, 2h, 4h, 8h, and 24 hrs
- Use the images to compare mitigation rates of cells
- Allow cell lines to grow and then count cells and split into the desired amount
- Take cell line place 2KD and 2ctr in media with serum and 2KD and 2CTR in serum-free media
- Incubate

Transwell Assay
Materials- D6P2T cells, Schwanoma (rat cell line)
Method

- Place SFM on top of well (.6ml), 10% FBS DMEM on bottom (100ul) and incubate for 1 hr w/ 5ug/ml Fibronectin
- Plate 2 wells for experiment and 1 for control (use water)
- Find desired

PC3 cell transient transfection with pSuperior+ GFP plasmids for shRNA knockdown of ABCA2
Materials
Plasmids- pSup 436, pSup 5198, pSup 5198 scr
Micropipettes, 12-well plate w/ cells, growth media, PLUS reagent, Opti-MEM media, Lipofectamine
Method

- Plate cells in 12-well format 2x10^5 cells/well in 1 ml media cell density should be 50- 80% after incubation.
- Remove growth media and replace w/ .5ml complete growth medium
- For each well to be transfected, dilute 1ug DNA in 200ul Opti-MEM media
- Mix PLUS reagent gently, then add 1 ul PLUS reagent directly to diluted DNA Mix and incubate for 10 min RT
- For each well, add 4ul of Lipofectamine LTX reagent to the diluted DNA solution, mix, and incubate for 30 min RT to form DNA- lipofectamine LTX complexes.

Results
The ABCA2 expression of Vimentin was found to be elevated in TRAMP prostatic epithelia when viewing the sample slides. In the dorsal prostate, ABCA2 expression in dorsal prostate was also elevated in TRAMP compared to WT mice; expression increases over time/progression. Increased oxidative stress markers were in KO TRAMP tissue.

Proliferation of prostatic & SV lesions was similar in WT and KO
TRAMP tissues. There was a slight elevation of ROS/RNS-induced DNA damage in
KO TRAMP prostate epithelia and an elevated ROS/RNS-induced 4-hydroxynonenal modified proteins. Seminal vesicle volume was greater in KO TRAMP mice at 20 weeks. Furthermore, normal stroma of KO TRAMP mice had elevated vimentin expression. No change occurred in the expression of desmin, a myocytic marker of stromal cells. As stated previously, the prostate tumor progression was similar, but incidence of metastatic tumors was elevated in WT and absent in KO. At 20 weeks, KO TRAMP had significantly larger SV volume than WT TRAMP. Whereas, tumor progression beyond 20 weeks, showed poorly differentiated tumors of the prostate. Normal stroma of KO TRAMP mice had elevated vimentin expression, but only a slight elevation in desmin expression, info via imaging the slides. SV tumors were shown to have similar levels of vimentin & desmin compared to WT. The scratch assays showed that KO mice migrated to heal the wound faster than the WT. The transwell assays, contradicted the scratch assays, by showing the WT cells, migrating through the pores, more than the KO cells.

Discussion and Conclusions

Prostate cancer has little to know symptoms, so in many, the cancer is not detected until it has progressed severely. This disease currently holds the position for an estimated 33% of all newly diagnosed cancers in men. Regrettably, the tumors caused by the disease do not always respond to the drugs or chemotherapy. Therefore, determining what causes the tumors to become resistant is important to efficiently treat the cancer. The role of ABCA2 expression is currently not understood, but in previous studies it has been linked with resistance to chemotherapy and multi-drugs. The Objectives were to determine if ABCA2 is correlated with tumor progression and to determine whether ABCA2 has an effect on the grade of prostate tumors and instances of metastasis. To examine the objectives, a knock out line was created using the Transgenic Adenocarcinoma of Mouse Prostate (TRAMP) model and compared to wild types by various methods including: Western Blotting Analysis, PCR, MRI imaging, Vimentin and Desmin analysis, Scratch Assays, and Transient Transfections. Although, prostate tumor progression was similar in both lines, the instances of metastases were elevated in the knock outs. This study increases our understanding of the role of a protein which could indeed be the link to revising treatments so that they will overcome the occurrences of multi-drug resistance and tumor relapse.

The Transgenic Adenocarcinoma of Mouse Prostate, TRAMP model, acquires progressive forms of prostate cancer. This model was used to generate the knockout mice from a gene-target disruption of the ABCA2 gene because it has been proven to work, successfully. In order to have specific controls and experimental groups, The TRAMP model was used to generate the knockout mice from a gene-target disruption of the ABCA2 gene. Using the Polymerase Chain Reaction (PCR) to amplify each mouse's DNA, distinguished which mouse was a Wild Type and which was a Knockout. After the Wild Type and Knockout mice were differentiated, MRI images were taken for up to 33 weeks to stage development and progression of prostate tumors.

At 20 weeks of development, the prostate tumors of KO formed and grew at a more accelerated rate than the WT but at 25wks the WT and KO lines both leveled at the same marking point. Western Blotting Analysis was used to verify the expression of ABCA2 protein located in the Wild Type mice versus the Knockout mice, and thus, determined the relative amount of protein and analyzed the results. Then the blots were probed for 4HNE to obtain an indication of the oxidative stress in comparison. Tissue sections of the genitourinary apparatus (GU) were affixed to slides in order to obtain relative measurements of Vimentin and Desmin. Vimentin and Desmin were markers used previously with the TRAMP model to indicate tumor progression in seminal vesicles. In contrast to the in vivo experiments, the KO cells were shown to express more Vimentin; an indication that KO cells were migrating more rapidly than the WT. Scratch Assays were also performed to compare the rate of migration between the WT and KO cells. The KO cells moved toward the scratch to repair the "wound" faster than the WT; thus, like the Vimentin analysis, demonstrated that the KO cells migrated at a more efficient rate, again contrasting the in vivo experiments.

Unfortunately, the D6P2T cells did not do as well as hoped with the transfections; future procedures could involve making improvements to the experimental design. Further investigation on determining the role of ABCA2, is a necessity. This finding could help improve treatments, thus, saving thousands of lives!

Crossing KO mice and TRAMP mice

Fig.1

Tg = transgenic + = positive for the ABCA2 gene - = lacks ABCA2 gene
Begin with: Tg/+ and +/+
Cross: Tg/+ and +/+ X -/-
½ of the offspring result as: Tg/+ and+/-
Cross: Tg/+ and+/- X -/-
All of the offspring result as: Tg/+ and -/-
Compare Tg/+ and ++ with Tg/+ and -/-

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Isolation and *ex vivo* expansion of CD8+ T cells

Background

The prostate is an exocrine gland present in the male mammalian reproductive system. It is located below the urinary bladder, directly in front of the rectum, and surrounds the urethra. The prostate stores and secretes a fluid that constitutes 25-30% of the volume of semen, adding to spermatozoa and seminal vesicle fluid. Prostatic fluid provides better motility, longer survival, and better protection of the genetic material to spermatozoa. The prostate also contains smooth muscles that help expel semen during ejaculation. Located just above the prostate are the seminal vesicles, glands that secrete about 60 percent of the fluid that makes up semen. Attached to the sides of the prostate are nerves that control erectile function.

The prostate needs male hormones (androgens) in order to work properly. Androgens are responsible for the sex characteristics in males. The main male hormone is testosterone, which is produced mainly by the testicles. Dihydrotestosterone specifically regulates the prostate.

Prostate cancer is the most common non-skin cancer in America, and affects 1 in 6 men. In 2009, more than 192,000 men will be diagnosed with prostate cancer, and more than 27,000 men will die from this disease. It is estimated that more than 2 million American men are currently living with prostate cancer. Prostate cancer occurs when cells within the prostate grown uncontrollably, creating small tumors. Prostate cancer is typically comprised of multiple small tumors within the prostate. If the prostate cancer is localized, it most times can be cured by treatments such as prostatectomy, radiation therapy, chemotherapy, cryosurgery, and hormonal therapy. Although there are usually treatment rates of 90 percent or better, these available treatments can damage surrounding organs which are very important to the quality of life in the process. Treatment strategies for this disease can disrupt normal urinary, bowel, and sexual function.

A prostatectomy is a procedure in which the diseased prostate is removed from the body. Although this procedure is very effective in eliminating prostate cancer, the removal of the organ causes damage to the surrounding areas. Urinary sphincters, which are bands of muscle tissue that regulate the flow of urine, may be damaged during the removal of the prostate. This can cause urinary incontinence or leakage. The erectile nerves may also be damaged during this process and may cause erectile dysfunction. The loss of the prostate and the seminal vesicles also leave these men infertile. These same effects take place with radiation therapy, in which the prostate and surrounding areas are receive radioactive exposure, and cryosurgery, in which the prostate is exposed to extreme cold in order to destroy abnormal or damaged tissue.

Chemotherapy is one of the most common treatments for almost any type of cancer. This is a treatment in which chemicals are used to kill cells that divide rapidly, which along with cancer cells affects cells of the bone marrow, digestive tract, and hair follicles, causing negative side effects such as a decreased production of blood cells, inflammation of the lining of the digestive tract, and hair loss.

Hormonal therapy can be a very effective treatment for prostate cancer initially, but also has many negative impacts on the patient's quality of life and does not effectively end the growth of prostate cancer long-term. Hormonal therapy in the treatment of cancer involves the administration of drugs which inhibit the production or activity of hormones. Because of the reduction of hormones, the patient may start to experience side effects common to those of women undergoing menopause, side effects such as impotence, hot flushes and sweating, weight gain, memory problems, and bone thinning. Prostate cancer cells initially respond to hormonal therapy, but can eventually mutate to become independent of those hormones that they initially depended on for growth.

Metastatic disease, or metastasis, occurs when cancer cells are transported through the lymphatic system and the bloodstream to other parts of the body, where they create secondary tumors. Once the cancer has spread beyond the prostate, risks of illnesses and death increase dramatically. There is no current treatment for metastatic prostate cancer.

We are studying T cell immunotherapy as a potential treatment for prostate cancer. The goal of immunotherapy for cancer is to make use of the immune system to eliminate malignant cells. Adoptive immunotherapy for cancer involves the isolation of antigen-specific T cells, and their *ex vivo* activation and expansion.

T cells are very important components of the adaptive immune system in the body. T cells are lymphocytes that mature in the thymus, and play a central role in cell-mediated immunity. There are several different types of T cells, which are distinguished by their functions. Helper T cells divide rapidly and secrete small proteins called cytokines that assist in an immune response. These cells express the glycoprotein CD4 on their surfaces. Cytotoxic T cells (CTLs) destroy virally infected cells and tumor cells and express the CD8 glycoprotein at their surfaces. Memory T cells are antigen-specific T cells that remain after an infection has resolves. They quickly expand upon re-exposure to their cognate antigen. These cells express either CD4 or CD8. Regulatory T cells shut down T cell-mediated immunity toward the end of an immune reaction and suppress auto-reactive T cells that escape from the process of negative selection in the thymus.

Cytotoxic T cells (CTLs) are activated when their receptors (T cell receptors, or TCRs) interact with molecules on the surfaces of antigen-presenting cells. Dendritic cells (DCs) are one class of antigen-presenting cells, which process antigen material and present it on their surfaces to cells such as CTLs. Immature DCs have low T cell activation potential, and mature DCs have much higher T cell activation potential. Prostate tumor cells have an elevated number of antigens at their surfaces such as PSMA (prostate-specific membrane antigen) and PSCA (prostate stem cell antigen) and PSA (prostate-specific antigen), which the DCs will engulf and present at their surfaces for the CTLs to recognize for activation.

Most prostate antigen-specific CTLs in the male body undergo a process known as “negative selection.” Negative selection removes thymocytes that are capable of strongly binding with “self” peptides presented by the MHC (major histocompatibility complex) on cells present in the body. These thymocytes receive an apoptotic signal that leads to cell death, and the majority of these cells die during this process. This process prevents the formation of self-reactive T cells that would otherwise be capable of generating autoimmune diseases.

Because these prostate antigen-specific CTLs with high affinity undergo this negative selection process, only low-affinity prostate antigen-specific CTLs are present when tumors form within the prostate. Because these CTLs have low binding affinity for the “self” peptides presented by the prostate tumor cells, they are unable to create an effective immune response towards these tumor cells.

Specific Aims

We want to ultimately construct a new method for the treatment of prostate cancer. We plan to begin raising high-affinity antigen-specific T cells from the peripheral blood lymphocytes (PBL) of an HLA-A2 (human leukocyte antigen-A2) female donor, and characterizing prostate tumor cell lines to be positive for HLA-A2 and PSMA and PSCA. Because the CTLs will be isolated from an HLA-A2 positive donor, they will be specific for the HLA-A2 serotype, and we want to facilitate the specificity of these cells for recognition of the prostate antigen peptides PSMA and PSCA using DCs that are pulsed with these peptides. We want to characterize our tumor cell lines for HLA-A2 and PSMA and/or PSCA so that the raised prostate antigen-specific CTLs will be reactive to these cell lines.

Hypothesis

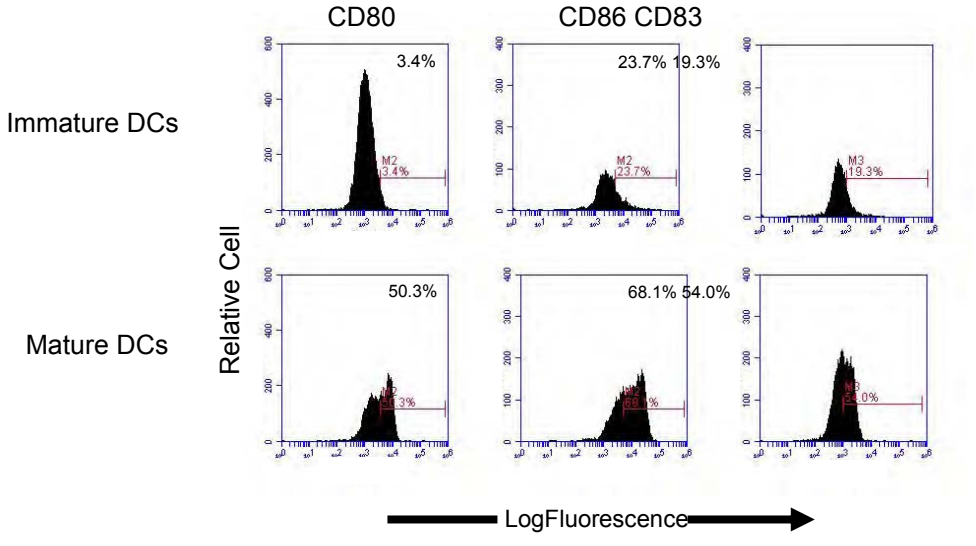
We believe that because the female body does not contain a prostate gland, high-affinity prostate antigen-specific CTLs, which are also present in the female body, will not undergo negative selection. For this reason we believe that the isolation and expansion of high-affinity prostate-specific CTLs will be easier from female donors than from males.

Methods

1) **Isolation of monocytes from the PBL of an HLA-A2 female donor.** We began by using frozen vials of blood that had been isolated from an HLA-A2 female donor.
2) **Preparation and maturation of DCs.** Vials of blood were thawed and placed into a 15ml tube with growth medium and centrifuged at 1000 rpm for ten minutes. The pellet, which contained the monocytes, was resuspended in growth medium and placed into a 6-well plate. Immature DCs were prepared and incubated for 5-7 days. After the 5-7 period, the DCs were matured and ready for pulsing with peptides after being placed in a 48-well plate.
3) **Isolation of CD8+ T cells from the monocytes.** CTLs were isolated from one well of thawed monocytes using the Dynabead CD8+ T cell isolation kit.
4) **Pulsing of DCs with PSMA and PSCA peptides.** Peptides for PSMA and PSCA were selected using the EpitOptimizer computer program which selected which peptides would have the highest binding ability with the T cell receptors.
5) **Co-culturing of DCs with CD8+ T cells in the presence of IL-15.** We co-culturing the isolated CD8+ T cells with the pulsed DCs in the 48-well plate and allowed them to incubate for 15 days, using IL-15 as a growth agent for the CD8+ T cells to expand.
6) **Flow cytometric analysis of cytokine secretion from CD8+ T cells.** We used Flow Cytometry to analyze the secretion of interferon gamma (IFN-γ) from the CD8+ T cells to note their activation.
7) **Phenotyping of prostate tumor cell lines LAPC-4 and LNCaP for HLA-A2 and PSMA and PSCA**. Also using Flow Cytometry, we characterized the two tumor cell lines for HLA-A2 expression and PSMA and/or PSCA expression.

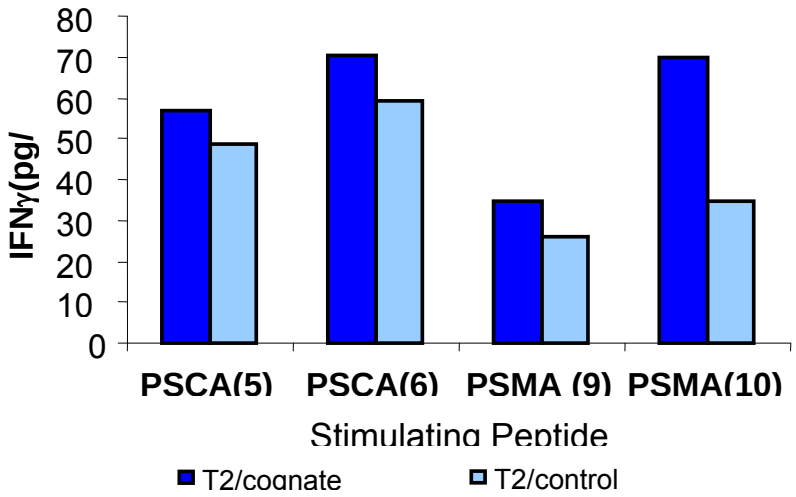
Results

Phenotype of PBL-Derived Dendritic Cells Used to Stimulate Prostate Cancer



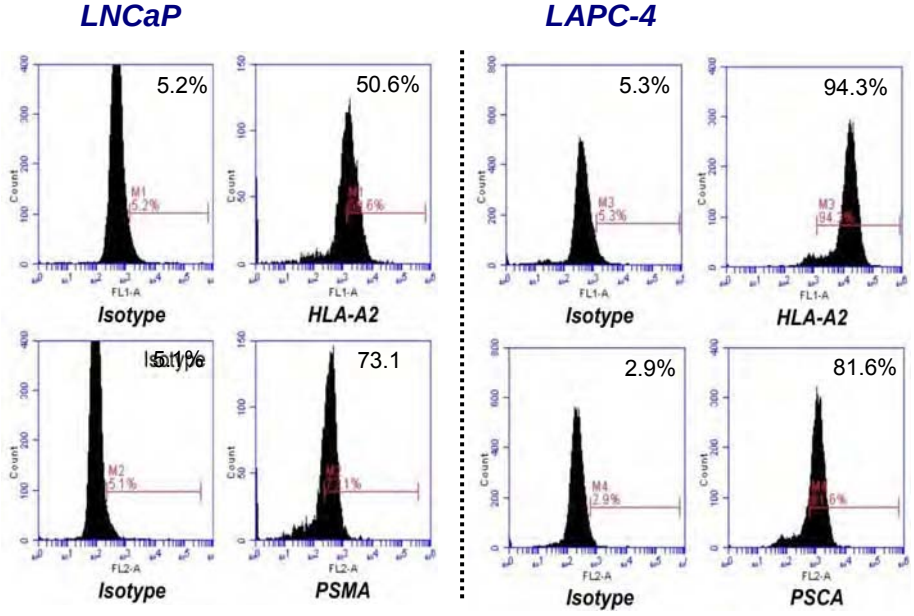
The increase in CD80, CD86, and CD83 were used as markers for the differentiation of the DCs from immature to mature.

Antigen Recognition by Female T cells Stimulated with Prostate Cancer Specific Peptide



Antigen recognition by CTLs using peptides for PSCA and PSMA and control peptides. IFN-γ secretion was measuring to analyze the activation of the T cells specific for these prostate cancer peptides. CTLs specific for peptide 10 (PSMA) showed a significant increase in IFN-γ secretion.

Characterization of prostate specific tumor cell lines



Characterization of prostate specific tumor lines using Flow Cytometry

Conclusion

In conclusion, our hypothesis was correct using Peptide 10 (PSMA). We were able to raise CTLs specific for the PSMA peptide. We were also able to characterize the prostate specific tumor lines LNCaP and LAPC-4, which were HLA-A2 and PSMA and HLA-A2 and PSCA positive respectively.

Discussion

We were able to raise prostate antigen-specific CTLs and characterize the prostate tumor cell lines for HLA-A2 and PSMA and HLA-A2 and PSCA expression as we had hoped to. We now plan to move forward in attempting to isolate CD8+ T cells from male donors to compare the activation and expansion against a female donor, and to eventually clone these CTL receptors for use in the patient's immune system.

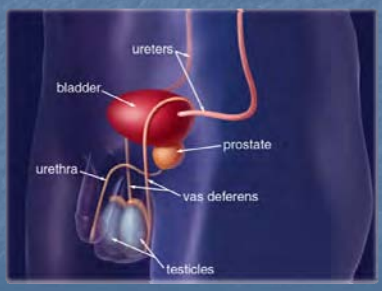
APPENDIX D.

Student Fellow Scientific Presentations

Does the Preoperative Evaluation of Men with Bladder Obstruction Affect the Outcomes of Outlet Reduction Procedures

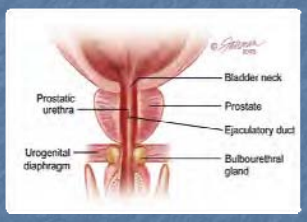
Presented By: Scharan Clarke
S.U.R.Program Participant 2009 at MUSC
DOD Grant: Marvella Ford, PhD
MUSC: Harry Clarke, MD, PhD, Stephen Savage, MD and Matthew McIntyre, MD

Anatomy



Prostate Anatomy

- Helps condition ejaculate
- Located between the bladder and external urethra
- Where genital and urinary tracts meet

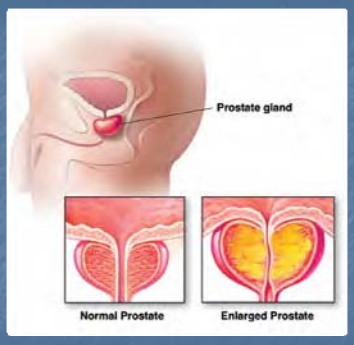


Terminology

- **Benign Prostate Hyperplasia (BPH)**
- **Bladder Outlet Obstruction (BOO)**
- **Lower Urinary Tract Symptoms (LUTS)**
- **International Prostate Symptom Score (IPSS)**
- **Quality of Life (QOL)**
- **Digital Rectal Exam (DRE)**
- **Prostate Specific Antigen (PSA)**
- **5-Alpha Reductase Inhibitor**
- **Alpha Blocker**
- **Transurethral Resection of Prostate (TURP)**
- **Greenlight Photovaporization of Prostate (PVP)**

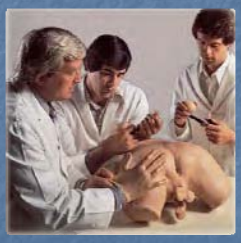
Benign Prostate Hyperplasia (BPH)

- BPH is a conglomerate of signs that, coupled with LUTS, develop in the male population as a result of aging and (BOO)
  - Microscopic BPH refers to the histoligic changes in the prostatic tissue
  - Macroscopic BPH refers to an enlarged prostate.
  - Clinically BPH includes LUTS, poor bladder emptying, urinary retention, an overactive bladder, urinary tract infection (UTI) and rarely now renal insufficiency



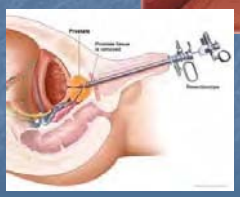
Diagnosis

- DRE
- Examination of the external genitalia area
- IPSS and QOL
- Uroflowmetry
- PVR



Treatment

- 5-alpha reductase inhibitors can cause prostate to grow slowly
- Alpha blockers allows urine to flow out of the bladder more easily
- TURP
- Greenlight PVP



Objective

- Evaluate whether preoperative workup affects surgical outcomes in patients with symptomatic urinary obstruction.
- We evaluated our series to see if we had clinically significant outcome differences.

Methods

- We retrospectively reviewed our series of 119 patients extracted randomly from 2004 to 2009.
  - Preoperative factors: IPSS, cystometrogram (CMG) or noninvasive uroflow, incontinence, retention, prostate size, and use of medical therapy.
  - Intraoperative factors: surgical procedure, operative time, hospital stay, catheterization time, complications, and the presence of an intravesical lobe.
  - Postoperatively factors: IPSS, noninvasive uroflow, recatheterization, reinitiating of medical treatments, de novo incontinence, and follow up.

Results

- We found 119 patients who had undergone outlet reducing procedures.
  - Nine patients were excluded from the study because obstruction was secondary to malignant processes.
- 68 (57%) underwent TURP and 51 (43%) underwent PVP of the prostate.

Results: Preoperative

Averages	CMG 32 (29%)	Noninvasive Uroflow 35 (32%)	No Testing 43 (39%)
IPSS	20.4	19.5	16
QOL	3.17	3.89	2.41
PVR	199 cc	153 cc	
Prostate Size	48 cc	44 cc	52 cc
Incontinence	2 (6%)	2 (6%)	2 (6%)
Retention	9 (28%)	2 (6%)	3 (7%)
Medical Therapy	24 (75%)	32 (91%)	29 (67%)

Results: Intraoperative

Averages	CMG 32 (29%)	Noninvasive Uroflow 35 (32%)	No Testing 43 (39%)
Operative Time	59 min	55 min	67 min
Hospital Stay	.96 days	0.4 days	1.2 days
Cath. Time	1.9 days	1.2 days	1.3 days
Complications	0	2 (6%)	2 (5%)

Results: Postoperative

Averages	CMG 32 (29%)	Noninvasive Uroflow 35 (32%)	No Testing 43 (39%)
IPSS	11.2	10	9.4
QOL	1.9	2.1	1.88
PVR	119 cc	118 cc	90 cc
Mean Peak Flow	13 mL/sec	11.7 mL/sec	9 mL/sec
Denovo Incontinence	0	1 (2%)	0
Reinitiation of Medical Therapy	5 (15%)	4 (11%)	1 (2%)
Follow Up	15.7 months	20 months	16 months

Conclusion

In our series more invasive preoperative evaluation did not lead to better clinical outcomes. Thus our hypothesis was disapproved.

** Further study will need to be completed due to the small number of patients in this series.

Acknowledgements

- MUSC SURP program (Debbie Shoemaker)
- Urology Dept: Dr. Harry Clarke
  Dr. Stephen Savage
  Dr. Matthew McIntyre and other residents
- DOD Grant (Dr. Marvella Ford and Melanie Sweat)

Questions

Enhancing Gene Delivery to Cancer Cells

Andrea S. Gibson

August 6, 2009

Dr. Christina Voelkel-Johnson
Department of Microbiology and Immunology
Medical University of South Carolina
Summer Undergraduate Research Program

Prostate Cancer
Introduction

- Cancer that forms in tissues of the prostate
- The prostate is a gland in the male reproductive system found below the bladder and in front of the rectum
- The American Cancer Society has estimated that in the year 2009 alone that there will be 192,280 new cases of prostate cancer and 27,360 deaths

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Prostate Cancer
Introduction

- Treatments for prostate cancer
  - Localized Cancer
    - Radiation
    - Surgery
    - Watchful Waiting
  - Advanced Cancer
    - Hormone Ablation (works for about 18 months)
  - Metastatic Cancer
    - Chemotherapy (not curative, but controls pain)
- HDACi and polymers have become a new way of treating cancer through gene therapy

HDACi
Introduction

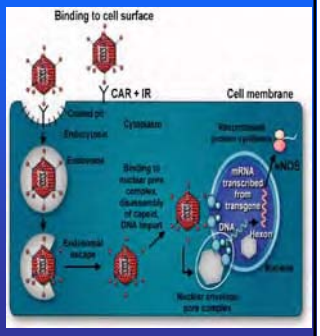
- Histone deacetylase inhibitors
- Exciting new class of potential anticancer agents for the treatment of solid and hematological malignancies
- In recent years, they have been known to cause apoptosis of tumor cells in culture and in animal models
- HDAC inhibition causes acetylated nuclear histones to accumulate in both tumor and normal tissues, providing a surrogate marker for the biological activity of HDACi in vivo (Visgushin and Coombes, 2002)

Polymers
Introduction

- Polymers are an arrangement of replicated structural units normally connected by covalent bonds
- Polymers have been utilized to improve “adenovirus-mediated gene delivery”
- Previous studies have shown that cationic polymers have enhanced adenoviral infection, but because of their toxicity, have a limited use (Kasman et al. 2009)

Background
What is an adenovirus?

- Is a DNA containing virus which can cause respiratory disease
- Can also be genetically modified and used in gene therapy
- Are commonly used due to the fact that they can infect many different cell types with high effectiveness
- Enters a cell by a surface protein known as coxsackie and adenovirus receptor (CAR) that functions as an adhesion protein (Voelkel-Johnson et al. 2009)



Background (cont.)
Previous Studies

- HDACi depsipeptide and MS275 enhance TRAIL gene therapy of LNCaP prostate cancer cells without adverse effects in normal prostate epithelial cells (Kasman et al 2007)
- Another study showed that polymers enhance adenoviral transduction of CAR-negative bladder cancer cells using the polymer EGDE-3,3' (Voelkel-Johnson et al. 2009)

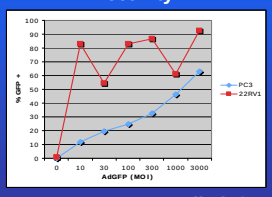
Hypothesis

- HDACi, MS275 and depsipeptide, will increase the infectivity of cells with the adenovirus AdGFP
- Polymer EGDE-3,3' will enhance the infectivity of prostate cancer cells along with the adenovirus AdGFP

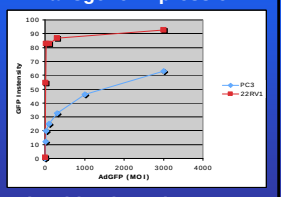
Results

Figure 1. Adenoviral infectivity

A Infectivity



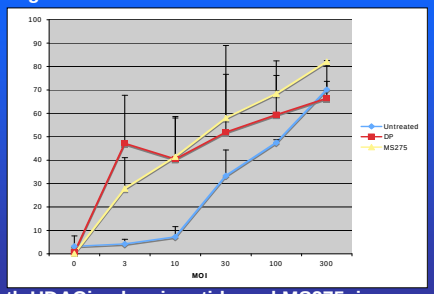
B Transgene Expression



Prostate cancer cells infect poorly with adenovirus and were therefore used as a model to test the hypothesis

Results

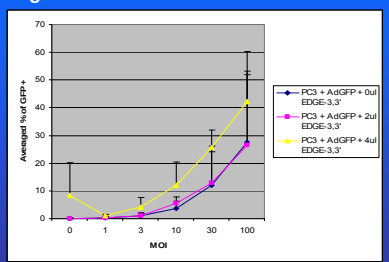
Figure 2



Both HDACis, depsipeptide and MS275, improved adenoviral infectivity, especially at low MOI's which are more clinically relevant

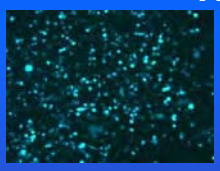
Results

Figure 3

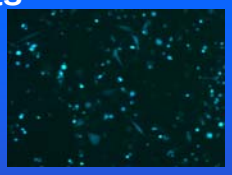


PC3 cells were plated overnight and were infected with a virus-polymer mixture. As a result, it was noticed that polymers did not enhance the infectivity of cells with AdGFP.

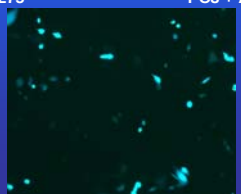
Results



PC3 + AdGFP + MS275



PC3 + AdGFP + DP



PC3 + AdGFP + EGDE-3,3'

Discussion and Conclusion

- PC3 cells were identified as a model to test the hypothesis
- HDACi enhanced gene delivery
- Additionally, there was a notable increase of infectivity in the cells that were treated with AdGFP and MS275
- EGDE polymer did not enhance gene delivery – perhaps it will be necessary to test other polymers for efficiency

Future Studies

- Future studies should include another cell line
- There should be an investigation as to why the polymer did not work as well in the prostate cancer cells experiment as it did with the bladder cancer cells in previous study

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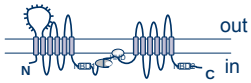
Questions?

Role of ABCA2 in Prostate Tumor Progression

CoDanielle Green
Townsend/ Tew Labs

ABCA2



- Normal tissues:
  - CNS, PNS, macrophages
- Member of the ATP Binding Cassette Transporter Protein family
- Associated with drug resistance
- Elevated in Cancers

ABCA2 deficiency in the Transgenic Adenocarcinoma of the Mouse Prostate (TRAMP) Model

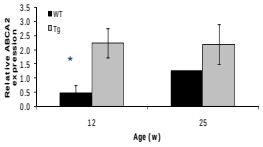
Overall incidence of metastasis in TRAMP mice from 20-25 weeks

ABCA2 genotype	Lung	Liver	Lymph Node	Mammary
WT	2/8	0/8	3/8	1/8
KO	0/7	0/7	0/7	0/7

•No difference in primary prostate tumor progression

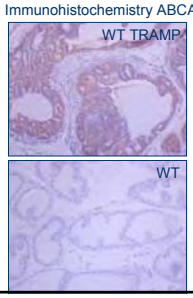
ABCA2 in TRAMP model

ABCA2 Western densitometry



•* P> .02

Immunohistochemistry ABCA2



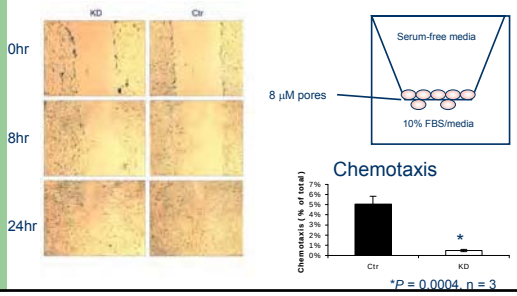
Objective

- Determine if ABCA2 has a role in prostate tumor progression and metastatic phenotype in mouse (TRAMP/ ABCA2 knockout) and cell (D6P2T and PC3 knockdown) models.

shRNA-based Knockdown of ABCA2 in cells with High ABCA2 Expression

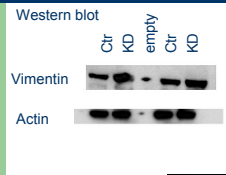
- D6P2T cells (rat schwannoma) stable knockdown (KD) (75- 80% of mRNA and protein compared to control shRNA (Ctr)
- PC3 cells (human prostate cancer) Transient transfection with shRNA constructs (sh-1, sh-2) and scrambled (Scr) control

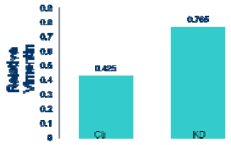
Wound Healing & Transwell Assays (D6P2T cells)



*P = 0.0004, n = 3

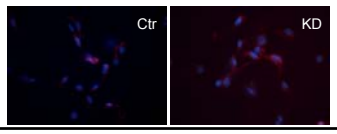
Vimentin expression is elevated in ABCA2 knockdown (KD) D6P2T cells





Vimentin (red)

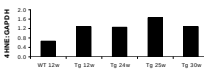
DAPI (blue) nuclei



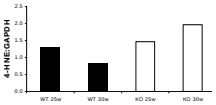
Conclusion

- In mice,
  - ABCA2 expression in dorsal prostate is elevated in TRAMP compared to WT mice; expression increases over time.
  - Prostate tumor progression is similar, but incidence of metastatic tumors is elevated.
- In D6P2T cells,
  - ABCA2 knockdown significantly inhibits chemotaxis in a transwell assay.
  - However, expression of vimentin (marker of EMT) in KD is elevated.
- These experiments were also performed in the PC3 cells, but further study is needed to determine the role of ABCA2 knockdown in prostate cancer cell chemotaxis.

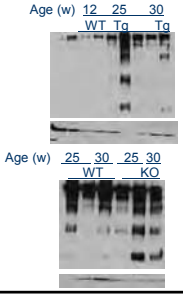
Elevated ROS/RNS-induced 4-hydroxynonenal modified proteins



4HNE-proteins increase over time in TRAMP dorsal Prostate



4HNE-proteins elevated in KO TRAMP dorsal prostate compared to WT



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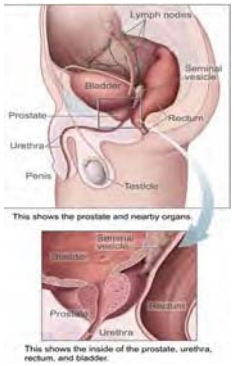
Isolation and *ex vivo* expansion of prostate antigen-specific $CD8^+$ T cells

Samantha Jones

Department of Defense (DOD) HBCU Collaborative Undergraduate Research Program, Student Undergraduate Research Program (SURP), South Carolina State University.

The prostate

- The human prostate is present in males and is responsible for the storage and secretion of a fluid that constitutes 25-30% of the volume of semen.
- The normal size of the prostate is about the size of a walnut and surrounds the urethra just below the urinary bladder.



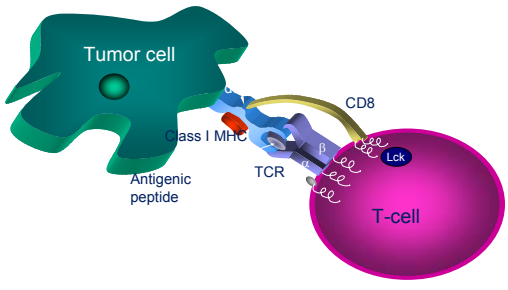
Background on Prostate Cancer

- Prostate cancer is the second most common type of cancer in American men, and a leading cause of cancer-related deaths.
- There are many different types of treatments available for prostate cancer.
  - Prostatectomy
  - Radiation therapy
  - Chemotherapy
  - Cryosurgery
  - Hormonal therapy
- These therapies may negatively affect the quality of life for the patients.
- There are currently no reliable treatments for metastatic prostate cancer.

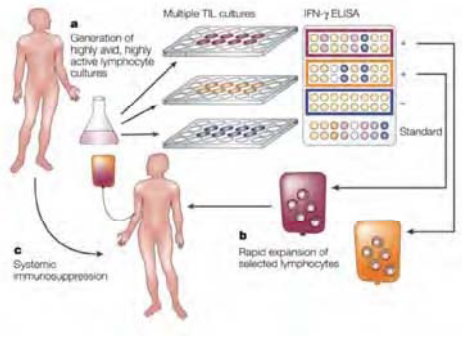
Immunotherapy for cancer

- The ultimate goal of immunotherapy of cancer is to make use of the immune system to eliminate malignant cells.
- Adoptive T cell immunotherapy for cancer involves the isolation of antigen-specific cells and their *ex vivo* expansion and activation.
- T cells are very important to the adaptive immune system in the body.
  - Are derived from the thymus
  - T cells are able to destroy infections and tumors
  - Can be activated by professional antigen presenting cell as dendritic cells (DCs)

MHC Class I Restricted Tumor Recognition



Adoptive Immunotherapy of cancer



Hypothesis

- Prostate reactive CD8⁺ T cells from HLA-A2 females will have higher affinity than those from males.
- Prostate reactive CD8⁺ T cells from HLA-A2 females are more easily expanded than from males.

Specific Aims

- To raise prostate antigen-specific CD8⁺ T cells (CTLs) from the blood of females
  - PSMA – prostate specific membrane antigen
  - PSCA – prostate specific stem cell antigen
- To characterize prostate specific tumor lines
  - HLA-A2 Expression
  - PSCA or PSMA Expression

PSMA and PSCA

- Prostate-specific membrane antigen (PSMA) and prostate stem cell antigen (PSCA)
  - Expressed prostate tumor antigens
  - Peptides are predicted to be immunogenic

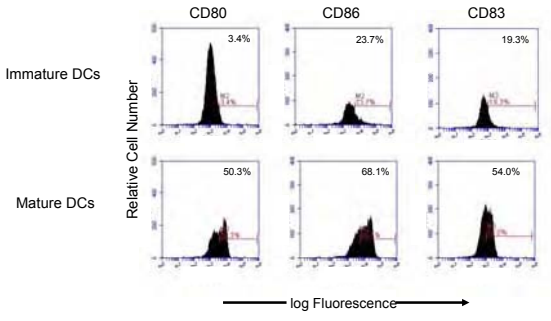
Peptide No.	Position	Sequence	Modifications
PSCA optimized peptides for HLA-A2 binding			
5	43	QLGEQCWTA	none
6	43	QLGEQCWTV	A51V
7	112	ALGLLLWGP	none
8	112	ALGLLLWGV	P120V
PSMA optimized peptides for HLA-A2 binding			
9	142	SLFEPPPPG	none
10	142	SLFEPPPPV	G150V
13	707	GIYDALFDI	none
14	707	YIYDALFDI	G707Y

Table 1: Sequence of peptides used for expansion of prostate specific CTL.

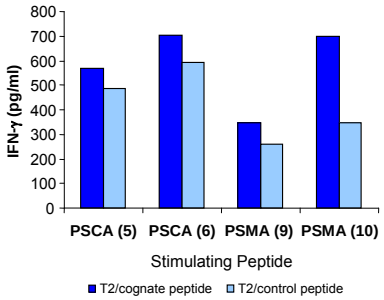
Methods

- Preparation and maturation of DCs and isolation of CD8⁺ T cells from the blood of HLA-A2 female donors
- Load DC's with peptides PSMA and PSCA
- Co-culture peptide loaded DC's with CD8⁺ T cells in presence of IL-15
- Testing for expansion of CTL specific for prostate cancer antigens

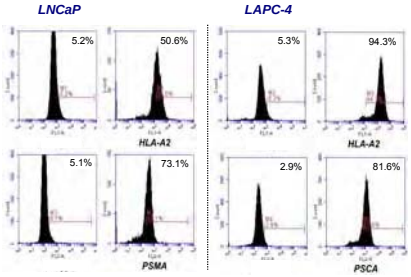
Phenotype of PBL-Derived Dendritic Cells Used to Stimulate Prostate Cancer Specific T cells



Antigen Recognition by Female T cells Stimulated with Prostate Cancer Specific Peptide Loaded DC



Characterization of prostate specific tumor cell lines



Conclusions

- CD8+ T cells were able to be expanded from an HLA-A2 female donor
- Tumor cell lines LNCaP and LAPC-4 were identified to be HLA-A2 and PSMA or PSCA positive

Acknowledgements

Aerial view of MUSC campus

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